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BRUCELLA INFECTION AND UNDULANT FEVER IN MAN



JEFFERY ALLEN MARSTON

An Assistant Surgeon in the Royal Artillery who first described Mediterranean fever as a separate disease in 1859

BRUCELLA INFECTION AND UNDULANT FEVER IN MAN

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TO ALL PATIENTS PAST AND PRESENT WITH
UNDIAGNOSED UNDULANT FEVER
THIS BOOK IS DEDICATED

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PREFACE

In 1928, at a meeting of the Office Internationale d'Hygiène Publique in Paris, it was reported that cases of undulant fever due to *Brucella abortus* had been discovered in Denmark and France, and the question was raised of whether such cases occurred also in the United Kingdom, as the prevalence here of contagious abortion of cattle, due to the same organism, was well known In consequence I was entrusted by my chief, Sir George Newman, Chief Medical Officer, Ministry of Health, with the investigation of this possibility and in August 1929 was published my report [82], in which I showed that, apart from cases originating abroad, which were mostly due to the *melitensis* variety of the organism, and laboratory infections, at least fourteen cases apparently of endemic origin had occurred up to that time in England and Wales

So started an investigation which I have carried on ever since with the help of general practitioners, consultants, pathologists, veterinarians, and others, for whose whole-hearted co-operation I am deeply grateful, resulting in the collection of the particulars of a large number of cases of undulant fever From this series I have used the first 1,500 indigenous cases, excluding laboratory infections, as the clinical basis of the present work The particulars obtained in different cases necessarily vary greatly in their completeness, but the number involved is sufficient to furnish a fairly complete picture of most aspects of the disease as it occurs in this country

As will be seen, the clinical disease, even when due to the same species of *Brucella*, varies considerably in different countries In order, therefore, to make this book widely useful I have, where necessary, drawn attention to such local variations It would, of course, be impracticable in a work of this size to give full clinical [illegible]

giving an account of *Brucella* infection in man, its origin, the nature of the infecting organism, the clinical features of the disease it may produce, its pathology, prevention, diagnosis, prognosis and treatment

As, however, animals form, with negligible exceptions, the sole reservoir of infection, a short account of the disease in different animals is an essential ingredient of this work, as is also the truly remarkable history of *Brucella* and its depredations.

At this point I would warn the reader that the picture of undulant fever which I have painted, based on my series of cases, will necessarily vary somewhat from accounts given by some other authors, not only because of local variations in the character of the disease, but also on account of the criteria which have been applied in making a diagnosis of *Brucella* infection. This important consideration I have discussed at the beginning of the chapter on Diagnosis [CHAPTER 8, p. 95] and I would only remark here that whilst too facile criteria confuse the picture and mislead the physician, too exclusive an attitude will leave many patients floundering in uncertainty or exposed to the stigma of neurosis or the unpleasant or even dangerous consequences of unwarranted treatment, including surgery.

Now since I started my study of this disease in 1929 the whole conception of infectious disease, and consequently of its treatment, has changed, at any rate among those who have frankly examined their ideas in the light of modern knowledge. No longer can we regard a potentially pathogenic micro-organism as an enemy to be cast out root and branch whatever the cost, but rather is infectious disease to be regarded as due to a disturbance of the host-parasite relationship, so that the object of treatment is rather to establish or re-establish a 'comfortable symbiosis' than to eradicate the parasite at any cost, a cost which may include permanent injury to or even death of the patient. In no disease, I believe, is this more true than in the subject of this book and I have therefore attempted to preserve this modern viewpoint throughout, though, in our present state of ignorance of the true nature of 'infection', and the body's reaction to it, such a task is by no means an easy one.

It is the fashion nowadays to refer to the human disease due to *Brucella* as 'brucellosis', the same term being applied to the disease in animals. I have, however, preferred to call the human disease by its old name of 'undulant fever' because of its historical associations, the very different character of the disease in man and in animals, and the fact that, at any rate in my series of cases, wherever a continuous temperature chart has been kept the typical undulations have occurred at some stage of the disease in the majority of cases [p. 64]. The fact that very occasionally a patient may have other

symptoms but no fever (only 5 of my 1,500 cases) does not invalidate the argument. In fact I think that all the arguments for the retention of the name undulant fever used by the International Congress of Medicine, held in London in 1913, are still valid, viz. 'it had priorly been used by Hughes in 1897; it does not limit the distribution of the disease [this is a reference, of course, to the old name Malta fever], it draws attention to one of the most frequent clinical signs; it is euphonious, and is easily applicable to any language'.

The literature on this subject is voluminous, but in the bibliography I have listed only those books and papers which give authority for the statements I have made or which will give the reader an opportunity, if he so desires, of obtaining fuller information on such points as cannot be fully set out here for lack of space.

In devising the Index I have tried to make it easy to find all the matter—and to find it quickly.

I wish to acknowledge my deep indebtedness to all those medical practitioners, medical officers of health, and pathologists who have so kindly supplied me with material for these studies during the past thirty years, and more especially to Dr. G S Wilson, Director of the Public Health Laboratory Service of the Medical Research Council; to all my friends in the veterinary profession who have supplied information and advice regarding brucella infection in animals, and especially to Dr A W Stableforth, Director of the Central Veterinary Laboratory (Ministry of Agriculture, Fisheries, and Food), Weybridge, who looked through Chapter 3 and gave me his valuable comments; to the Commandant and Librarian of the Royal Army Medical College, Millbank, for supplying me with the photographs of Surgeon-General Marston, and Sir William Horrocks, to Professor Debono of Malta for giving me the photograph of Sir Themistocles Zammit, to the Librarians of the Royal Society of Medicine and the Royal College of Veterinary Surgeons for their help in tracing literature, to Dr Wesley W Spink of the University of Minnesota for permission to reproduce the skiagrams of brucella spondylitis (FIG 18) from his invaluable treatise *The Nature of Brucellosis*, to the Director of the Agricultural Research Council's Field Station, Compton, Berkshire, and Dr. A McDiarmid, for supplying me with the photographs reproduced in FIGURES 8 and 19, to Professor Lord Stamp of the Postgraduate Medical School, London, for the microphotograph of

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Br. melitensis (FIG. 6); to Dr. F. Fulton of the London School of Hygiene and Tropical Medicine for the microphotograph reproduced in FIGURE 10; to the Royal Society of Tropical Medicine and Hygiene, for permission to reproduce the photograph of Sir David and Lady Bruce, which appeared in their Transactions (FIG. 2); and finally to innumerable friends in all parts of the world who have supplied me with valuable information and reprints of papers

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July 1959

THE HISTORY OF BRUCELLA INFECTION IN ANIMALS AND MAN

It will be convenient in considering the history of this disease to deal with animals and man separately up to the point at which the connection between the two was realised. Thereafter they may well be taken together.

ANIMALS

It is surprising how little attempt appears to have been made to elucidate the early history of contagious abortion in cattle or diseases due to *Brucella* in animals of other species The earliest reference which, it has been suggested, refers to abortion due to *Brucella* is in Genesis (Ch 31, v 38) where Jacob, defending himself to Laban, claims that for the twenty years he has been with him Laban's ewes and she-goats have not cast their young, but this is obviously open to other interpretations Other references to abortion in animals are just as elusive, e g Aristotle (382–322 B C) [4] says that an excess of acorns is said to cause abortion in both pigs and sheep Fleming [122] thinks that the desolating epidemic following the Tarentian war, which carried off women and cattle at Rome in large numbers, was probably brucellosis, and certainly the description he quotes would fit nor was this outbreak, it appears, a solitary one After this comes a very large gap, till in the late eighteenth century there are accounts of outbreaks of enzootic abortion among cows and sows in Germany, and among cows and mares in France [285] In France in 1804, according to Nocard and Leclainche [273] quoting Flandin the peasants were 'so convinced that these abortions are contagious that they always say that, in order to avoid recurrences, the calves must be carefully wrapped up and taken out by the window or a hole in the wall, but not by the door, and especial care must be taken that no cow follows it or goes by the path which it has taken'

It is not until the nineteenth century that there are any records of enzootics of the disease among cattle in Great Britain, when it was a cause of extensive loss to the stock-owner Thus John Lawrence [216], writing in 1805, says 'cows are well known to be much given

to abortion, slinking, or slipping their calves; in an early period of gestation it is sometimes epidemic; and thence people have supposed it even contagious'. The *Complete Farmer* (1807) also refers to abortion as contagious. In 1837 there was an enzoötic affecting bovines, sheep, and mares and after this the prevalence of the disease is often commented on.

In the United States of America the first accounts seem to have appeared about 1864 [176]. Here, as in Europe, the contagious nature of the disease was suggested but never proved.

Then in 1895 Bang [8] and Stribolt found a very small Gram-negative bacillus in the thick yellow exude between the wall of the uterus and the foetal membranes, and were able to grow it in pure culture. This organism required a reduced partial pressure of oxygen for its growth, unlike Bruce's *Micrococcus melitensis* which grew aerobically. Bang confirmed the causative nature of his bacillus by reproducing the disease in healthy, pregnant heifers. The connection between contagious abortion of cattle and undulant fever in man, however, lay twenty-three years ahead [p 11]. In 1909 Bang's work was confirmed in England by McFadyean and Stockman [237], though curiously enough, as Spink notes, the authors thought it unlikely that the bacillus was excreted in cow's milk and it was not, apparently, until 1913 that it was grown from the milk of cows artificially infected [385]

MAN

The date of emergence of most infectious diseases, or in other words the date on which an innocent saprophyte took to crime, is always difficult to determine and *Brucella* is no exception to this rule. When considering old sources it is the continued fevers characterised by heavy sweats, enlargement of the spleen and frequent relapses which engage our attention and excite our suspicions, but these characters are hardly sufficient to identify with any certainty such a disease as undulant fever, in the absence of bacteriological or serological evidence

Hughes [FIG 1] in his famous monograph [181] seems inclined to give some weight to the opinion of Adams in his 1849 translation of the *Epidemics* of Hippocrates (*ca* 450 B.C.) that the fevers there described corresponded exactly to those prevailing in Greece at the time at which Adams was writing, only ten years before Marston's [246] description of 'Mediterranean or Gastric Remittent Fever'



FIG 1 SURGEON-MAJOR MATTHEW LOUIS HUGHES, 1867-1899
His classical monograph on undulant fever was published in 1897

Certainly Hughes believed that Torti's [358] 'febre subcontinua' (1712), Burnett's [44] 'Mediterranean Fever' (1816), and the 'Common Continued Fever' of Hennen [167], Davy [91], and others (1817—35) were in fact undulant fever

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FIG 2 SIR DAVID and LADY BRUCE
Sir David Bruce discovered the causative organism in undulant fever

There was, however, great confusion until 1859 when J. A Marston [*Frontispiece*], then an Assistant Surgeon in the Royal Artillery and eventually a Surgeon-General and P.M O. of the British Forces in Egypt, by giving a clear account of this clinical

entity at last rescued undulant fever from the rubbish heap of the *Continued Fevers* This achievement by a young doctor, remarkable as it was, did not, however, lead to an immediate simplification of nomenclature and Hughes, writing in 1897, was able to give forty-six synonyms used by different authors subsequent to the publication of Marston's paper, the favourites being *Malta Fever* and *Rock* or *Gibraltar Fever*

Up to 1886 the aetiology of the disease was quite unknown but in 1884 David Bruce [FIG 2], who had just passed out of the Army Medical College at Netley (head of the list), was drafted to Malta where he at once recognised the importance of Malta fever, and 'Stimulated thereto by the importunities of his wife' [116] set to work to discover its cause and soon noted the presence of minute cocci in fresh preparations of spleen pulp taken at autopsy In 1886, while home on leave, Bruce prepared sections of spleen tissue to show the micro-organisms that he had noted in fresh specimens and Sims Woodhead, in whose laboratory he was working, thought they would prove to be the cause of the disease On Bruce's return to Malta he tried, with Scichluna, to grow the organism, but it was not until July 1887 that a fatal case occurred in a young soldier and gave him the chance of removing the spleen aseptically ten minutes after death and at last isolating his micrococcus [38] Shortly afterwards he grew it from the spleen blood obtained during life and he succeeded in reproducing the disease in monkeys

This was a splendid achievement, an unknown but important part of which was due to the skill of Mrs Bruce, who was, unlike her distinguished husband, a brilliant microscopist and was in 1931 elected by the Royal Microscopical Society an Honorary Fellow, an unique distinction for a woman Bruce called his organism *Micrococcus melitensis*, but it has since been renamed in his honour *Brucella melitensis*

The next landmark in the history of this disease was the publication in 1897 of Hughes' monograph, to which I have already referred and which in the opinion of all who have made a serious study of this subject deserves to be numbered among the great classical descriptions of disease on account of its clarity, conciseness, completeness, acute observation and sound judgement For all these reasons it did much to advance the study of undulant fever In 1895, as I have already noted, Professor Bang of Copenhagen showed that contagious abortion of cattle was due to a small bacillus which he



FIG 3 SIR THEMISTOCLES ZAMMIT
He found agglutinins for *M melitensis* in the blood of Maltese goats

named *Bacillus abortus* and which, twenty-three years later, was shown by Alice Evans [112] to be a variety of the same organism which Bruce had shown to be the cause of human undulant fever.

[illegible]

animals, as well as in that of newly infected patients.

Then in 1904 the Royal Society appointed a Commission [250],



FIG 4 SIR WILLIAM HORROCKS
He grew *M melitensis* from the milk of Maltese goats

at the instance of His Majesty's Government and with the concurrence of the Army, the Navy and the Governor of Malta, to investigate the prevalence of Mediterranean fever among the Forces of the Crown in Malta. The personnel of this Commission was

[illegible]

found that the blood serum of five out of six goats which he intended for experimental infection with *M. melitensis*, but which had *not* been infected by him, agglutinated the organism to a high titre. No sooner had this observation been fully confirmed when, on 21 June, Major (later Sir William) Horrocks [FIG 4] found the microbe in large numbers in the milk of a naturally infected goat and further investigations showed that about 40 per cent. of the goats in the island had agglutinins for the organism in their blood and that numbers of apparently healthy goats in each herd were excreting *M. melitensis* in their milk. This discovery resulted in the famous order of 1906 to the naval and military forces in Malta forbidding the consumption of unboiled goat's milk, with the consequent reduction of the disease among them to negligible proportions: one of the most dramatic demonstrations of an epidemiological truth on record.

Unfortunately the civil population of Malta did not profit by this example and have, therefore, continued to suffer from undulant fever, though steps are now being taken to rid the island of this infection. Goat's milk, and later sheep's milk, were subsequently shown to be the cause of the disease in France, Italy, Algeria and other Mediterranean countries In 1908 Danlos, Wurtz, and Tanon [89] reported the first two cases of undulant fever in France, first diagnosed as typhoid fever and contracted from a herd of goats suffering from an enzootic thought to be strongylosis. The agglutination tests, on which the diagnosis was chiefly made, were carried out by Charles Nicolle among others. In 1911 Cantaloube [47], a French general practitioner, reported an investigation he had carried out of an epizootic of goats characterised by abortions which had broken out in a district of the Cevennes, in the Department of Gard, this outbreak being closely followed by the occurrence of a febrile illness in humans which, at first thought to be typhoid fever or influenza, was eventually shown by agglutination tests to be undulant fever, as indeed Cantaloube had suspected from the begin-

ning. This is a masterly demonstration of epidemiological methods by one who describes himself modestly as 'only a country practitioner, without any experience of scientific publication'. The source of the trouble is traced with unerring aim to goats which had been covered in September or October at a single farm where, in accordance with local custom, they had been sent for a time from valleys which, though in geographical proximity, were isolated by the natural features of the country.

So far only goats and sheep had been incriminated, not cows; in fact Cantaloube advised his patients to substitute cow's for goat's milk (and to eschew goat's milk cheese), but in 1912 Weil and Ménard [367] reported a case with strong presumptive evidence of infection by cow's milk, but drew no conclusions from this important finding.

In 1914 Kennedy [207], then a Captain in the Royal Army Medical Corps, found agglutinins for brucella in the milk and blood of London cows and urged that the possibility of a *melitensis* infection of cows in this country should not be lightly thrust aside, remarking that he had heard of two cases of undulant fever in persons who had never been out of England. His son told me that Captain Kennedy was very anxious to follow up his findings, but the First World War intervened and the opportunity never recurred. Bassett-Smith [11], checking up on Kennedy's findings, reported that 'cow's milk in some cases has a natural tendency to agglutinate the *M. melitensis*, but if care is taken most of these non-specific reactions may be avoided', so this distinguished worker, lacking the clue provided four years later by Alice Evans, rejected Kennedy's evidence because he could not explain it and so missed the opportunity of making an important discovery.

FURTHER EVIDENCE OF HUMAN AND ANIMAL BRUCELLOSIS

Up to 1918 contagious abortion of cattle was regarded as an entirely different disease from that which produced abortions in goats and sheep and consequently no human disease was attributed to the known presence of Bang's bacillus in the milk of many herds. For instance when Byam [46] reported a case in England in that year he assumed that the organism was the *M. melitensis* and that the patient had acquired the infection from goat's milk, though the patient



FIG 5 ALICE EVANS

She showed the relationship of the *B abortus* of Bang to the *M melitensis* of Bruce

declared that he had never drunk such milk, nor had he been out of England since 1898

The whole outlook was, therefore, dramatically changed by Alice Evans' [FIG 5] brilliant demonstration [112] in 1918 of the very close resemblance existing between the *B abortus*, which Bang had shown to be the cause of contagious abortion in cattle, and the *M. melitensis*, shown by Bruce to be the cause of undulant fever in man In the paper describing this work Alice Evans raised the question of whether human disease might not be caused by drinking cow's milk containing *B abortus* and in 1921 this question was again raised by Bevan [20], working in Rhodesia where contagious abortion was common, who found an agglutinin titre of 1 in 200 for *B. abortus* in the blood serum of a patient with undulant fever. It was, however, left for Keefer [204] to establish the truth of this occurrence by growing an organism belonging to the *B. abortus* group from the blood of a patient in Johns Hopkins Hospital, Baltimore, U.S A This work was carried out in 1922 but not published until 1924, a few months before Orpen [277] in Rhodesia showed by agglutinin absorption tests that it was the *abortus* and not the *melitensis* variety of *Brucella* which caused undulant fever in that country. This was the beginning of a flood of reports which have since demonstrated the existence of undulant fever of animal origin in every continent and in most lands where cattle, goats or sheep are kept

No historical consideration of brucella infections is complete without telling the dramatic story of the S S *Joshua Nicholson*, because of the light it throws on the nature of the disease in the goat, the transmission of infection from animal to man, and the manner in which such infection may, on previous occasions, have been introduced into the United States of America The dramatic element is due to the fact that the Mediterranean Fever Commission's yet unpublished findings were made available to the United States authorities just too late to avoid this incident, but just in time to prevent a worse catastrophe On 19 August 1905 this steamer, the *Joshua Nicholson*, plying between Egypt and Antwerp took on board at Malta a herd of goats, of which sixty-one were milch goats, which had been collected by Mr George F Thompson, representing the U S Bureau of Animal Industry, for export to that country with a view to increasing the production there of goat's milk for the use of invalids and children These goats had been specially selected and were all apparently in good health None of the ship's company went

ashore at Malta, where the ship stayed only a few hours. On the passage to Antwerp, whence the goats were destined for the U.S.A. in another ship, their milk was freely drunk by most of the ship's company, the officers drinking 'mixed milk' collected in a large vessel, and the crew 'whole milk' from a single goat per man, but the second mate and the cabin boy drank very little of this milk and the two engineers boiled theirs. At Antwerp three members of the crew went to hospital with a provisional diagnosis of Malta fever. Another eleven crew members left the ship at Antwerp and went on a fortnight later to London, of whom eight fell ill at intervals varying from eighteen to thirty-four days from the date of embarkation of the goats and five were found to have brucella agglutinins in their blood serum. All the four persons mentioned above who had consumed very little goat's milk, or had boiled it, escaped The goats, after five days in quarantine in Antwerp, were transhipped in the S S. *St. Andrew* bound for New York and none of the people in this ship (crew of thirty-six officers and men, thirty cattle men, three goatherds and Mr. Thompson) developed Malta fever, though Mr. Thompson, who refused to believe that goat's milk could cause Malta fever and continued to drink it, had complained of 'liver trouble' whilst on board the *Joshua Nicholson* and he died suddenly of pneumonia in January 1906. The goats on arrival at New York were transferred to the quarantine station at Athenia, N.J., where the causative organism was grown from the milk of several animals and eventually all the goats and their kids were destroyed In the meanwhile, unfortunately, some of the milk was given to an elderly woman at Athenia, in poor health, who contracted Malta fever. So ends a story which provides as pretty a demonstration of many of the features of brucella infection as any professor of this subject could have devised

2

THE NATURE OF BRUCELLA

GENUS

THE genus *Brucella* comprises *Br melitensis*, natural host goat and sheep, and formerly known as *Micrococcus melitensis* *Br. abortus*, natural host cow, formerly known as *Bacillus abortus*· *Br suis*, natural host pig; and *Br tularensis*, natural host rodents, such as ground-squirrels and jack-rabbits, in which it produces a plague-like disease, formerly known as *Bacterium tularense*. An organism newly discovered in diseased sheep in New Zealand, Australia, and California has been tentatively classified as belonging to this genus and has been named *Br ovis* This organism resembles *Brucella* morphologically, is aerobic, Gram-negative and requires an increased partial pressure of CO_2 for growth It has so far been described only in non-smooth phases and does not agglutinate in antisera prepared against the smooth phases of the classical *Brucella* species Strains isolated from the desert wood rat (*Neomata lepida*) in Utah have also been claimed as belonging to a new *Brucella* species [46a, 245a]

All the recognised members of the genus give rise to undulant fever in man, except *Br tularensis*, which causes a very different disease called tularaemia when it occasionally affects man and is regarded by some workers as more appropriately assigned to the *Pasteurella* group For all these reasons it will not be considered further in this book (except briefly on p 104) Pacheco [279] has lately suggested that the clinical and pathological resemblances between glanders and brucellosis in the horse are so close that *Pf mallei* may well be a form of *Brucella*, but this suggestion at present lacks confirmatory evidence

As might be expected, I think, with an organism having so many hosts living under so many different climatic and nutritional conditions, many variants have arisen, some of which are not easily assignable to the species listed above, as will be shown when I consider presently the ways of differentiating these species For this reason there has always been, and still is, much difference of opinion as to the classification of *Brucella*, and indeed as to whether the differently behaving members of the group should be regarded as species or merely varieties, a confusion which was made worse in

the early days by failure to differentiate between smooth and rough phases, this failure resulting in the adoption of the names *para-abortus* and *para-melitensis* for certain strains which were inagglutinable, and are now known for merely rough variants of the *melitensis* and *abortus* types [282]. The species versus variety discussion can find no place in a work such as this and I therefore, for convenience, adopt the classification favoured by Wilson and Miles [376] and many other informed writers, though warning the reader that this arrangement cannot be regarded as in any way final[1]

Unfortunately all the tests devised for the differentiation of the species of *Brucella* detect quantitative rather than qualitative differences, so that the standardisation of such tests is of the utmost importance

Before describing the various characteristics of the *Brucella* species as seen in the laboratory, I would call attention to the great artificiality of our methods and the inevitable differences which must therefore exist between *Brucella* growing in the human body and the same organism growing in its own excrement, as E. G. D. Murray has pointed out.

MORPHOLOGY AND STAINING

In the following description I have chiefly followed Wilson and Miles. The organism is a short, slender, pleomorphic rod with round ends, the sides parallel or convex [FIG 6] The length varies between 0 6 and 1 5 μ, the breadth being 0 5 to 0 7 μ, so that they are smaller than any of the Gram-negative cocci. They are usually arranged singly, in pairs joined end-to-end, or in short chains Though *Br melitensis* [FIG. 6] is more coccal in form than *Br. abortus* it is impossible to distinguish morphologically with any certainty between individual strains, *Br abortus*, however, when grown on a relatively rich medium, often develops long, bacillary forms, 2 0 to 3 0 μ in length, whereas *Br. melitensis* remains coccal on the same medium

The organism stains fairly well with ordinary dyes, is Gram-negative, non-acid-fast and sometimes bipolar in staining. It is

¹ The two main views on this subject are set forth with great clarity in the recent

non-motile and non-sporing. Capsules are occasionally seen in freshly isolated cultures

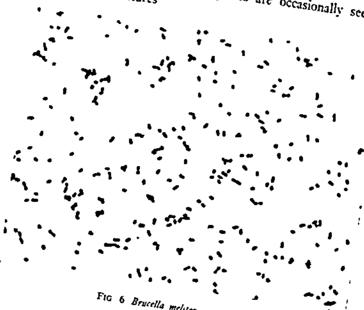


Fig 6 *Brucella melitensis*, × 1300

CULTURAL CHARACTERS

Brucella will grow on many media, both solid and liquid On agar the colonies are small, translucent and undifferentiated. In broth there is a moderate turbidity with a slight powdery or viscous sediment, which disintegrates completely on shaking *Brucella* grows poorly on gelatine but well on potato, where it develops a yellowish colour in two to three days, deepening in a fortnight to *café au lait* or chocolate

The appearance of the colonies differs according to whether the strain is smooth or rough Smooth strains of *Br abortus* on potato agar are small, bluish and translucent, with regular margins and a smooth, glistening surface, the individual cells appearing under the microscope as uniformly short rods arranged singly Colonies of rough strains are about the same in size as those of the smooth strains but are more opaque, less convex and have a dull, granular look, whilst the individual cells are usually somewhat longer The colonial differences are intensified on glycerol glucose agar.

SPECIES AND THEIR DIFFERENTIATION

The three species of *Brucella* with which we are here concerned, viz. *melitensis*, *abortus* and *suis* are, for all practical purposes, indistinguishable morphologically and the following are the principal properties on which differentiation depends.

RESPIRATORY REQUIREMENTS. An interesting and important species difference is related to the respiratory behaviour of the organism, for typical *Br. abortus*, unlike *Br. melitensis* and *Br. suis*, usually requir[illegible] partial pressure of [illegible] being usually em[illegible] noted, however, that strains of *Br. abortus* occur, such as the Rhodesian strain, which grow well under aerobic conditions.

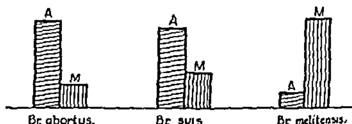


FIG. 7 Antigenic structure of *Brucella*

FERMENTATION. *Brucella* does not produce detectable fermentation of any of the sugars, with the exception of erythritol.

ANTIGENIC STRUCTURE. A great deal of work has been done on this since about 1908, but much of the early work was stultified by failure to distinguish between smooth and rough strains. If, however, as Wilson and Miles [375] showed, care is taken to [illegible] means [illegible]

FIG 7 gives a picture of the antigenic structure of the three species.

It will be seen that all three species contain both the A and the M antigen, the former being in excess in the *abortus* and *suis* species, the latter in *melitensis*. A monospecific serum can be prepared by adjusting the absorbing dose to the titre of the serum so as to absorb out all the minor agglutinins whilst leaving the major agglutinins almost intact This monospecific serum can then be used for direct agglutinin tests with an unknown type to determine the species to which it belongs (Renoux and Mahaffey [306] have produced

evidence of the existence of further antigens in *Brucella* and have illustrated their conception of the distribution of antigen by a [illegible]

[illegible] degree to which their growth is inhibited by the presence of certain dyes in the culture medium. These differences can be determined either by preparing separate agar plates containing the various dyes, or more conveniently by incorporating in liver-agar plates strips of filter paper impregnated with stronger solutions of the dyes and then streaking these plates transversely with suspensions of the strains to be tested. The growth of typical *Br. abortus* is inhibited by thionin but not by basic fuchsin, methyl violet, or pyronin; whereas *Br. suis* grows well in the presence of thionin but is inhibited by basic fuchsin, methyl violet, or pyronin *Br melitensis* can usually grow in the presence of any of these dyes For practical purposes it is sufficient to employ media incorporating thionin and basic fuchsin only, differentiating according to the scheme in TABLE 1.

TABLE 1

GROWTH OF BRUCELLA SPECIES ON DYE PLATES

SPECIES	THIONIN	BASIC FUCHSIN
Br abortus	—	+
Br suis	+	—
Br melitensis	+	+

As with other tests, this one is not conclusive as different strains of the same species differ considerably among themselves, e g some strains of *melitensis* grow very poorly on thionin, methyl violet or pyronin plates; strains of *abortus* from Southern Rhodesia are more resistant to thionin than strains from elsewhere; *suis* strains from Denmark are more susceptible to dyes than American strains, etc For this reason the dye test should be used in conjunction with other diagnostic procedures, when it will prove to be of considerable value.

HYDROGEN SULPHIDE PRODUCTION Another useful character for diagnosis is the different power of the species to produce H_2S when grown on liver agar Freshly isolated strains should be used and H_2S production determined by the employment of lead acetate papers *Br abortus* and *Br suis* (American variety) give off H_2S for at least four days, whereas *melitensis* either produces no H_2S, or does so for twenty-four hours only Here again the rule is

broken by varieties, for Danish *Br. suis* produces no H_2S, and strains of *abortus* and American *suis* sometimes lose this power quite quickly under laboratory conditions So that a given strain which fails to produce H_2S beyond the first day may yet be *abortus* or American [illegible]

[illegible]

facility with which the different *Brucella* species break down urea to liberate ammonia as a way of classifying isolated strains Thus if *Brucella* is grown in a substrate containing urea and a dye added to detect changes in pH due to this liberation of ammonia, it will be found that cultures of *Br. abortus* produce this change much more slowly than strains of *Br. melitensis* and *Br. suis*, but *melitensis* strains cannot be differentiated from those of *suis* by this means Here again individual strains varying from the type in their urease activity are not infrequent and this test is much less employed, even in conjunction with other tests, than was formerly the case.

[illegible]

dithiocarbamate (DETC) A thirty-six to forty-eight hour culture on liver or Albimi agar suspended in saline is spread on an Albimi agar plate and a paper disc of 11 mm. diameter, dipped in DETC, is placed in the middle. When examined after three days rings appear round the disc varying in appearance according to the species of *Brucella* in the culture. (For details of this test the original paper should be consulted)

SENSITIVITY TO ERYTHROMYCIN. Castañeda [59] found that the growth of *Br melitensis* and *Br. suis* was inhibited by only one-tenth of the concentration of erythromycin which was required to inhibit *Br. abortus*, and he therefore suggested that this method should be used for allocating unknown strains to the three species. Gargani [136] concluded from his own experiments that *Br suis* was the most sensitive to erythromycin, *Br. abortus* least sensitive, whilst *melitensis* strains behaved sometimes like *abortus* and sometimes like *suis*

BACTERIOPHAGE. Specific *Brucella* phage has been identified and its use suggested for distinguishing the different species, but the position is far from clear at present [283*a*, 286*a*]

ABERRANT STRAINS Though the occurrence of aberrant

strains of *Brucella* is of importance, nevertheless their frequency should not be exaggerated. Cruickshank [80] from an examination of 474 strains isolated in the United Kingdom concluded that the [illegible]

[illegible] disposal are sufficient only to classify strains into the three main categories, in each of which will be found individuals differing in one or more characteristics from the type strains Such differences may, at times, be of practical importance. Thus in April 1940 Menton, Director of the Emergency Public Health Service Laboratory at Stafford, isolated a *Brucella* from a guinea-pig which had been injected six weeks before with a sample of mixed milk from an accredited herd in the midlands. This organism grew aerobically on primary culture and, when examined by Wilson [373] at the headquarters' laboratory at Oxford, was identified as belonging to the *melitensis* species The Ministry of Agriculture and Fisheries was naturally alarmed by the danger presented to sheep and goats, as the Ministry of Health was by the danger to man, and intensive efforts were therefore made to trace and slaughter, under special powers conferred for the purpose by the Brucella Melitensis Order 1940, all the animals which had been in this herd at the time the milk sample was taken, and all such animals were in fact slaughtered, whilst a close watch was kept on the herds into which the potentially infected animals had been introduced This strain has, however, appeared during the intervening years in many parts of the country, and it is difficult not to regard it as an aberrant strain, in spite of its model behaviour in the laboratory, as no infection of goats, sheep or man has so far been traced to it.

The only other aberrant strain which need be mentioned here is that which Renoux [302] has named '*Brucella intermedia*'. This [illegible] tests like *Br. melitensis* (except that its urease activity is that of *Br. abo*[illegible]

str [illegible] established. Some workers consider, however, that such experiments demonstrate the possibility of natural mutation

3

ANIMAL RESERVOIRS OF INFECTION AND THE FATE OF BRUCELLA OUTSIDE THE BODY

THE ANIMAL RESERVOIRS OF INFECTION

THE main reservoirs of *Brucella* infection are in the animal world, undulant fever being the human disease resulting from transmission of the infection from animals to man (inter-human infection is practically unknown, see p. 45). Many animal species are known to carry the infection and to suffer disease in consequence, and it seems likely that more animal hosts will eventually be discovered, but the vast majority of human infections come from cattle, sheep, or goats. In Great Britain the only animal species ever shown to be infected are the bovine and equine. A single case of *Br. suis* infection, contracted in Eire, has been reported [269*a*].

GOAT

The great importance of the goat as a source of infection is due to the fact that this animal, which is hardy and can flourish under the most unpromising conditions, is the basis of the economy of large populations in both hemispheres, and in such countries it lives in very close contact with its owners, thus facilitating the transmission of infection. Unlike other domestic animals the goat harbours only the *melitensis* species of *Brucella*, but this is the most invasive of all Kids are highly resistant to infection during the first two months of life, but after two to three months a serum response to infection occurs in some individuals, and the older the kid the longer the response lasts [288] Though the idea has been prevalent that brucella infection in the goat gives few outward signs (the Report of the Mediterranean Fever Commission [250] hardly refers to the clinical disease in the goat), yet in no animal are these apt, at times, to be so conspicuous The disease usually begins like typhoid or typhus, or less frequently as a mild, febrile, influenza-like infection [56] In many animals fever sets in within forty-eight hours of general infection and, apart from the most obvious and important sign of infection, namely abortion, the animal loses condition, has a

dejected expression with a drooping head and staring coat, and perhaps slight diarrhoea.

The pregnant goat becomes uneasy and constantly bites at a point high up on the left flank, where, presumably, it feels pain. The milk changes are peculiar to this species, as infection is often so heavy that the milk becomes a clear serum with clots floating in it and the whey yields a pure confluent growth of *Br. melitensis*. Following abortion there is an infected vaginal discharge lasting two to three weeks and constituting the most active agent in the spread of the disease, which is favoured in some countries, such as France, by the annual migration of herds, from the plains to the mountains, in the summer (*transhumance*), the replenishment of herds by annual purchase from outside, unhygienic methods of milking, the size of herds, and the employment in many cases of a communal shepherd, involving the mixing of herds.

Localisation of infection, which begins during the second month after termination of the pregnancy during which infection occurred, does not, in most cases, seem to include the udder and uterus after the fifth month from kidding. Usually the termination of a second pregnancy after infection will not cause an exacerbation of the disease, but a small proportion of the animals will continue to excrete brucella in the genital secretions during the second lactation. Vaginal excretion is often, but not necessarily, associated with parturition and the organism may be found in the vaginal mucus of a goat which has never been pregnant, and such excretion may continue for at least three months after exposure. Vaginal discharge and urine are the common vehicles of infection, faeces playing a negligible part.

The routes of transmission between goats are not well understood at present, but the available data suggest that the most probable routes are through the mucous membranes of the alimentary and respiratory tracts, and of the eye.

As regards persistence of infection, recent studies have shown that only some goats become chronic carriers of *Br. melitensis* infection for the rest of their lives, the majority get rid of the infection. It is, however, the minority of chronically infected animals which keeps infection going in a herd. On the persistence of infection in immature goats the information at present available is rather contradictory and the Joint FAO/WHO Expert Committee on Brucellosis (referred to henceforth as the Expert Committee) has

recommended that this very important problem should be further investigated [197].

SHEEP

Brucella infection in sheep is a cause of serious economic loss in some countries, as well as a source of infection for the human population. In some Swiss parts of the Rhône valley, for instance, nearly a quarter of the population are, at any one time, in bed with undulant fever contracted from sheep [1] The infecting organism is nearly always *Br. melitensis* and in countries in which the disease is prevalent its methods of spread and clinical manifestations closely resemble those in goats. In other countries, however, sheep appear to be much more resistant to the infection, even when brucella infection in other species is widely prevalent, a difference which may be related to the breeds of sheep concerned It is interesting to note that in Argentina, where infection of sheep is rare, the organism isolated in such cases is nearly always *Br suis* [262]

Sheep rid themselves of the infection more easily than goats, though some sheep remain infected even after six months of sexual rest, and excretion of *Brucella* in the milk appears to be more continuous than in goats Infection tends to continue longer in ewes in non-endemic areas than in endemic areas. An appreciable number of infected sheep recover spontaneously [304] Most ewes which abort excrete the organism in their milk, sometimes for years, and the organism may be recovered from the vagina of aborting ewes, but it has never been isolated from the vaginal mucus of an ewe not carrying young

A remarkable disease, which seems to be peculiar to sheep, viz epididymitis of the ram associated with abortions in the female, is due to an organism which has been given the name *Brucella ovis* [39], though its classification as a *Brucella* should be regarded as provisional This disease is very prevalent in Australia and New Zealand, where it causes heavy losses in flocks of sheep A similar disease has been described in California [238]

CATTLE

The disease in cattle, known commonly today as contagious abortion and formerly in some countries as Bang's disease, has long presented

[1] Professor G Bouvier (personal communication)

a formidable challenge to the veterinarian and to public health workers in general, owing to the enormous economic loss and the serious amount of human disease which it causes In Great Britain, until the initiation of an intensive vaccination campaign, about 20 per cent of adult female bovines were infected with ***Br. abortus*** and contagious abortion caused greater loss to the dairying industry than



FIG 8 Placenta and membranes of a cow which aborted from *Br abortus* infection, showing necrotic and partly necrotic cotyledons and inter-cotyledonary thickening of the membrane

any other disease In the United States of America in 1947 about 5 per cent of the adult cows were affected, coming from about 20 per cent of the herds in the country, and the annual economic loss from this disease was estimated at about £3½ million [339] The corresponding figure for Switzerland today is about £1½ million [1]

Infection is usually introduced into healthy herds by infected pregnant cows which, when aborting or during normal parturition and for up to a month afterwards, discharge large numbers of organisms with the liquor amnii and the foetal membranes. The ordinary channel of infection on farms seems to be contamination of

[1] Professor G Bouvier (personal communication)

byres, straw, fodder, and drinking water by such products, the placenta [FIG. 8], and the dead foetus, but the contamination of pasture is also important, *Brucella* retaining its vitality for long periods outside the body, even when exposed to the weather [p. 33]. Infected bulls also play a part, though usually a minor one, in the spread of the disease, and the conveyance of infection by artificial insemination with infected semen can be important.



FIG 9 Section of the allantochorionic membrane of a similar placenta Several of the trophoblast cells covering the membrane are dark and granular owing to the intracellular accumulation of *Br abortus* The adjacent inter-cotyledonary space contains an exudate which appears in the section as a mass of cell debris This also contains enormous numbers of *Br abortus*

It has been demonstrated that cattle can be infected by ingestion, through the conjunctiva, through the broken or unbroken skin, and per vaginam, as well as artificially by injection In view of the irregularity with which humans contract infection from infected milk it is interesting to note that the same thing is true of bovines. For instance Bang and Bendixen, and Buck and Cotton failed to infect cows by giving them infected milk to drink [182], and Frei [130] recorded an incident in the Zurich Animals Hospital in which a cow consumed a foetus which had previously been shown to be heavily infected, yet the cow did not become infected. The foetus

of an infected cow easily becomes infected and the organism has been grown with great regularity from the lungs and digestive tracts of aborted foetuses. Young calves, on the other hand, are relatively resistant to infection, and even when they are fed on infected milk and the lymph glands draining the mouth and pharynx become infected, yet five or six weeks after the calves are taken off their diet of infected milk the organisms have disappeared from these glands [48]

Pregnant animals are more susceptible to infection than others and susceptibility to infection increases with the approach of sexual maturity. Some protection is afforded by infection preceding abortion and after repeated abortions this protection may become permanent. On the other hand the calf infected at an early age is not necessarily immune and calves born of infected mothers are usually susceptible on reaching maturity

On the first introduction of the disease into a herd abortions may occur only at long intervals, and the infection is seldom detected until a considerable time has elapsed During this interval some apparently healthy animals may be producing milk containing *Brucella*, and thus perhaps give rise to human cases of undulant fever An outbreak may, however, run a very acute course if there has been no previous infection in the herd and the animals are fully susceptible

Abortion occurs usually at seven or eight months, sometimes as early as five months, but it is important to remember that many animals, though infected, calve at or near full-term and that these

then contains large numbers of *Brucella*, though some animals never excrete them via the udder, even when they have aborted Most animals, however, excrete them in the colostrum About half of the animals excreting *Brucella* in the milk never do so again, the rest excrete for a few weeks or months, or occasionally for a year or more [342]

minated by abortion, or by sterility, or finally by normal breeding without abortions

Though, as has been noted, excretion of the organism in the milk

may continue for months or even years, excretion in the urine and faeces is usually short lived. All infected animals do not excrete the organism in their milk, but they must all be regarded as potential sources of infection by this means.

An important part in the spread of *Brucella* infection in cattle is played by 'carrier herds', the cows of which give birth to normal calves at full term, so that infection is not suspected by the owner, but these animals produce infected milk and this infection spreads to other cows in the herd, despite the use of S 19 vaccine.

The *abortus* species of *Brucella* is the one specially pathogenic for bovines, but infection can occur with all three species and they have all been found in natural infections of many different species of animals in addition to bovines

SWINE

Swine can contract infection with any one of the three species of *Brucella* and can transmit the infection to man and other animals. In the United Kingdom no evidence of swine infection has ever been found, though Doyle [102] found *Brucella* agglutinins to a titre of 1 in 100 in four sows out of 10,474 slaughtered and thought at the time that this must signify existing or recent *Brucella* infection.

In other countries, however, such as Denmark, the United States, Germany, Australia, Egypt, and Russia swine infection has presented a serious problem In Denmark the disease was first recorded in 1929 [18, 355], when it caused a rapidly spreading enzootic. Two subsequent and similar enzootics started in 1940 and in 1951 respectively, and, curiously enough, each time in the same veterinary practice (hares were suspected as the source of infection, see p. 28) The organism isolated was what is known as Danish *Br. suis*, differing from the American *Br. suis* by forming no hydrogen sulphide on culture, or only very slowly No human infections have ever been traced to this Danish strain, but swine have been found there infected with typical *Br. abortus* In the U.S.A. the species most commonly infecting swine is *Br. suis* [233], the American strain, which is highly invasive for man [158], and recently this strain has been isolated from an aborted swine foetus in France [363] But natural infection of swine with *Br. abortus* has been found frequently in the U S A [233], the Argentine [262], and elsewhere. Even in Iowa, where *Br suis* infection has been so common in swine and in man, twelve different strains of *Br. melitensis* were isolated

and carefully identified [28] In spite of the commonness of swine infection, experimental infection of these animals has proved very difficult, both with *Br. suis* [34] and *Br. melitensis* [352], some breeds of pig being especially resistant. On the other hand Otero [278], working with volunteers, found *Br suis* to be highly virulent for man.

The natural disease in swine differs from that in cattle, and in man, in a lesser susceptibility to infection during pregnancy, the frequency with which animals infected when young will overcome the infection on reaching maturity, and the important role of the boar in the spread of infection [355, 383] Infection is contracted via the alimentary tract, genitalia, skin, and conjunctiva The organisms tend to localize in the lymph glands, especially the

sterility is common even in the absence of abortion In the boar orchitis, epididymitis, prostatitis, and sterility are common results of infection Infection of the urine is frequent and often very persistent.

HORSE

Veterinary literature contains many reports of *Brucella* infection in horses, in which the organism almost invariably plays a pyogenic role The infection seems to be contracted from cattle or their excreta and Schoop [318] has suggested that the use of horse blankets for cattle and afterwards for horses, putting horses in cattle stalls, and giving raw milk from infected cows to foals and young horses, are the usual modes of transmission, though attempts by other workers [121] to infect horses experimentally by feeding, intravenous injection, scratching the skin of the withers, and by injection into the eye failed

The characteristic lesions in horses are poll evil and fistulous

in suppuration Infected mares sometimes abort and the organism (usually *Br abortus*) may be isolated from the foetus [239, 243] Infected horses sometimes excrete the organism in their faeces and

instance of horse to man infection, though the Mediterranean Fever Commission described three cases in soldiers in which ponies, with *Brucella* agglutinins in their blood, were believed to be the source of infection [234]

HARE

The existence of *Brucella* infection in the hare was not suspected until 1936 [33] when Fluckiger reported a suspected case with agglutinins in the blood serum [311] A second case was reported in Switzerland in 1944 [311] and this time the organism was isolated by guinea-pig inoculation. Retrospectively the authors consider that cases reported by Bollinger in 1874 and by Burgi in 1904, and attributed respectively to 'hare syphilis' and to 'a staphylococcal infection, alone or associated with other organisms', may well have been brucellosis

Of 1,941 hares whose blood serum was examined in Denmark in 1954 and 1955, 4·2 per cent. had either agglutination, or complement-fixation, positive [69] Meanwhile, in 1950, an infected hare had been found in France [185] and soon after others were found [186, 187]. A single case was also reported from Germany in 1941 [379], and in 1956 seven more [131]. One case was reported in Czechoslovakia in 1952 [272].

It is of interest to note the species of *Brucella* concerned in these cases In the Swiss cases the species seems to have been *suis*, of the Danish type, though Burgisser [40] considers that the organisms isolated from his cases were of a variety specific for hares, but probably derived from *Br abortus* by passage in hares. The Danish cases were due to *suis* of the Danish type. In the first German case the species was *abortus*, but in the later ones it was *suis* of the Danish type Of the French strains six out of eight resembled *suis* (of the Danish or the American type), one was more like *melitensis*, and the other one was eventually typed as *abortus* Jacotot and Vallée [187] concluded that as there was no swine brucellosis in France and *Br. suis* had never been isolated from swine there (but see p 26), the hares must have been infected by domestic animals or humans, and that the biochemical and antigenic characters of the organism must have become modified in the body of the hare towards the *suis* type Though the truth of this contention cannot be proved or disproved at present, it is, nevertheless, of great interest in view of the many varieties of *Brucella* now known and the unexpected appearance of new types, such as the *melitensis* strain in England [p. 19].

Another interesting aspect of brucellosis in the hare is the role played by it in the spread of infection to domestic animals I have already referred to the three Danish enzootics in swine, all starting in the same district [p. 26] The evidence implicating hares as the source of all these outbreaks is very convincing [18], and it may well be that the part played by this and other wild animals in the spread of infection has been underestimated. Among such other wild animals the rat and the rabbit have been found infected and although no wild animals infected with *Brucella* have been detected in the United Kingdom, yet it is at least suggestive that the Brucella Committee of the Agricultural Research Council found —before the Second World War—that herds that had been freed from infection and were believed to be efficiently protected from reinfection, often became reinfected within two years, suggesting the conveyance of infection by infected wild animals or birds though mechanical conveyance is, of course, another possibility

The lesions in leprine brucellosis are usually roundish, flat nodules, well delimited, yellow or slightly brown in colour and of varying size. The contents are either of the consistency of putty or are soft, caseous and necrotic. The organs most often affected are the uterus, testis, mammary glands and spleen; the liver, lungs and lymph glands being less frequently involved. The testes, epididymis, and spleen may be enormously enlarged and filled with abscesses and necrotic nodules The differential diagnosis between brucellosis and pseudotuberculosis or staphylomycosis can only be made by culture of the organism or serological tests

RABBIT

Brucella infection of the wild rabbit has been reported from Argentina [327], France [104, 286, 352], and of the domestic rabbit from Tunisia [307] The species concerned in two of the French cases and in the Argentine cases was *melitensis*, whilst in the Tunisian cases it was '*Br intermedia*' [p. 19] The organs involved were the spleen, which contained multiple abscesses, lymph glands, lungs, with miliary granulations, liver, and bone marrow.

RAT

Shaw [324], of the Mediterranean Fever Commission, found agglutinins for *Brucella* to a titre of 1 in 30 in some rats in Malta,

but failed to grow the organism from their organs, and more extensive investigations by other members of the Commission were all negative [117] Menton [251], in England, had the same lack of success with 201 wild rats, many from infected farms, or abattoirs in which infected cattle had been slaughtered, and in the laboratory these animals showed a high resistance to artificial infection, a fact confirmed by Bosworth [29] However Dubois [104] stated that infection of wild rats occurred in France, and in the U.S S R. Karkadinowsky [202] reported that *Brucella* had been isolated from eleven wild rats (from the blood of one; blood, liver and kidneys of two; liver alone of two; liver and spleen of five; and spleen alone of one) The isolation of *Brucella* from the kidneys of two of these rats is worth noting and Bosworth found that the urine of artificially infected rats sometimes contained the organism, so that foodstuffs of man and animals could be contaminated by this means.

DOG

Dogs are often exposed to infection on farms and elsewhere and have been seen to consume infected foetuses and placentae, but considering the frequency of their exposure the number of proved cases of *Brucella* infection in dogs which have been reported is strikingly small Members of the Mediterranean Fever Commission examined forty-six stray dogs in Malta [117], and although the blood serum of three agglutinated the organism to a low titre, they failed to isolate *Brucella* from the organs of these animals Later, however, Kennedy [206] succeeded in growing it from the organs of one dog out of 114 examined and he says that at least nine 'showed unmistakable signs of infection'.

There have been four recent reports of such recovery, three from a dog [226, 287, 369] and one from a bitch [268], as well as three cases, the first and most serious in 1922, in which aborting bitches were believed on serological grounds to be infected and to have passed on the infection to humans [90, 159, 249] Specific agglutinins have also been found in the blood of many dogs in Argentina [327] and Eritrea [71]

It should not be forgotten that dogs, apart from communicating the disease directly to other animals and man, may also play a significant role in spreading the disease by their habit of dragging infected matter, such as aborted foetuses, from one place to another.

CAT

The evidence with regard to infection of cats is even scantier than that for dogs Shaw [324] found specific agglutinins in the blood of five out of twenty-two cats examined in Malta, and in one case he isolated *Br. melitensis* from the mesenteric glands

CHAMOIS

[illegible]

corneal ulcer of one chamois and from an intracranial abscess, secondary to an eye infection, of another chamois

ELK ('MOOSE', NORTH AMERICA)

Br. abortus was grown from the blood of a bull elk by Katz [203] and from the pleural and pericardial fluids of a young female by other workers [193] In addition Rush [314] found three out of thirty-two animals in an elk herd close to an infected buffalo range positive to the serum agglutination test

BISON ('BUFFALO', NORTH AMERICA)

Creech [78] and Katz [203] both isolated *Br abortus* from the testes of male bisons, and Moore [266] and also Rush [314] have found specific agglutinins in the blood of many of these animals

INDIAN BUFFALO (BUBALUS BUBALUS)

This animal has been found to be infected in the Campania of Italy [139] (the only part of the country in which it is reared), the infecting species being *Br abortus*

OTHER ANIMALS

The evidence of *Brucella* infection in other animals is purely [illegible]

(human infections being traced to two of the mules reported by the last authors)

BIRDS

As regards the *fowl* Huddleson and Emmel [177] claimed to have infected fowls experimentally and to have found natural infection in individual birds, but their evidence, and that of Dubois [103], is very inconclusive and later workers all failed to confirm their results. All the same it is well established that the fowl can be infected with *Brucella* and harbour it for a considerable period, though there are usually no signs or symptoms of disease [151]

Galuzo and Rementzova [134] isolated *Brucella* from the hooded crow, *Corvus cornix*, as well as the rook, *Corvus frugilegus*, and infected experimentally the house sparrow, *Passer domesticus*, and [illegible]

certain number of positive sero-diagnostic tests with blood from the heart of English sparrows

TRANSMISSION OF INFECTION BY INSECTS

The possible role of insects in the transmission of infection was investigated by the Mediterranean Fever Commission [250] Though Horrocks was unsuccessful in his attempts to transmit infection by mosquitoes fed on infected human patients and monkeys, he refers to a successful experiment of this kind carried out by Zammit (he gives no reference, but says that forty-eight hours intervened between the absorption of the organisms and their transfer to the patient) and he remarks that his own lack of success does not invalidate Zammit's result [174]

Another group of the Commission's workers succeeded in transmitting infection to a single monkey by a mosquito [117], but McCullough and Weir [234], summing up all the evidence, confessed that they could find no evidence of the transmission of infection to man through the agency of mosquitoes or other biting insects, though the organism can live in these insects for four or five days

Galuzo and Rementzova [134] found ten species of ticks in the U S S R and also a mosquito (*Culex pipiens*) to be naturally infected with *Brucella* In England Menton [251] examined twenty-one groups of insects, mostly flies, collected from infected farms, but they all failed to infect guinea-pigs on which they were fed Wellman [368], however, succeeded in transmitting *Brucella* infection by

means of *Musca domestica*, *Stomoxys calcitrans*, and other insects to guinea-pigs, cattle, pigs, and goats, though in the heifers so infected abortion did not occur

Cockroaches seem to be unimportant in this connection [313]. It seems impossible to exclude altogether the mechanical conveyance of infection by insects, though the evidence at present available does not suggest that this method is important.

TRANSMISSION OF INFECTION FROM MAN TO ANIMALS

Before leaving the subject of animal reservoirs of infection mention must be made of the fact that infection can travel in the opposite direction, i e. from man to animals, though such an occurrence is probably infrequent

Violle [364] has described what appears to be such an occurrence A shepherd contracted undulant fever from his infected flock, and when, a good while later, he was employed as shepherd of another and clean flock, a few months after his arrival abortions started in this flock and were attributed to him, as he was found to be excreting *Brucella* intermittently, though he was by that time in good health

THE FATE OF BRUCELLA OUTSIDE THE BODY

A knowledge of the length of survival of *Brucella* outside the body under different conditions is obviously of the greatest importance when considering the circumstances in which infection may be spread [CHAPTER 4] Survival in water and various foods is considered in Chapter 4 but the following additional evidence is of interest

This problem was investigated by the Mediterranean Fever Commission and Horrocks [173] found that *Br melitensis* survived in sterilized tap water for thirty-seven days, in Maltese soil, allowed to dry naturally, for forty-three days, in damp soil for seventy-two, and in sterilized sea water for twenty-five days Exposure to the sun, however, kills the organism in a few hours Kennedy [205] found that *Br melitensis* in the urine in which it had been excreted survived dried on cloth for seventeen days, in dust for less than thirteen days, and in sterile milk for sixteen days The organism derived from urine, when grown on media and added to 'Mediterranean fever urine' survived dried on cloth for fourteen days, dried in dust for forty-four days and mixed with sterile tap water

for twenty days. Shaw found that the same organism could survive in 'Malta fever urine' for forty-nine days; in urine dried on navy serge for seventy-eight days; in sterilized water for fifty days; in unsterile sea water for forty-six days; and in sterilized well manured soil for eighty-three days.

Pukh [295] has investigated the survival of *Br. abortus* in cattle yards and recovered it from wood scrapings of the cattle sheds for up to four months thirteen days, the time depending upon whether or not the selected areas were soiled with a layer of cattle faeces; on adjacent dung-covered ground, exposed to the sun, two weeks; on similar ground, shaded from the sun, thirty-four days. Pukh concluded that on cattle yard floors the organism might remain infective for a maximum of four to five months.

Kuzdas and Morse [213] investigating the survival of *Br. abortus* (U.S.D.A. strain 2308) in nature under controlled conditions found that it survived for periods of up to 824 days at 25°C. in bovine urine, lake water, tap water, raw milk, bovine faeces and two types of soil, but at 37°C. the survival time was at best a quarter of that at 25°C. and was sometimes only a few days.

King [209] found that a culture of the same organism embedded in a manure pit, the maximum temperature of which was 170°F. [76·7°C.] in summer and 158°F [70°C.] in winter, was non-viable four hours later

Survival of *Brucella* in refrigerated blood is considered in connection with interhuman infection [p. 47]

THE ORIGIN OF INFECTION IN MAN

For all practical purposes man always contracts the disease from animals, either directly or indirectly, for, as will be shown presently, inter-human infection is a mere curiosity.

The particular animal from which a human being is likely to be infected varies with the country or district in which he lives. In the United Kingdom the only source of infection is bovine; in France and most Mediterranean countries sheep and goats are also involved In Denmark swine are a source, but not to the same extent as in the hog raising state of Iowa, U.S A [158], where for the years 1930-5 inclusive 70 per cent. of the cases of undulant fever diagnosed were due to *Br. suis* In Central and South America goats are by far the most important reservoir of infection.

But whatever animal species is involved three main modes of infection occur, viz. consumption of infected animals and their products, direct or indirect contact with infected animals or their products, laboratory or inoculation infection, and possibly inter-human infection.

ALIMENTARY INFECTION

MEAT

The flesh of most animal species which harbour *Brucella* is usually consumed after sufficient cooking to kill the organism, the chief exception being pork sausages which are often eaten half cooked and sometimes even quite raw, especially by the workers preparing them Levine [220] reported seventeen cases in packing-house workers in Chicago who had eaten partly cooked meat or sausages, but in only three cases was the organism isolated of the *abortus* variety, the others being all *suis* The possibility of infection through the skin does not seem to have been excluded in these cases, but a rather more [illegible]

half cooked goat's meat contracted the disease. I know of no

evidence suggesting infection from meat in the United Kingdom. A very unusual mode of infection was reported by Loffler [223], a slaughterman having been infected by drinking raw swine's blood.

MILK

The principal animal products conveying the disease are, however, the milk of a cow, goat or ewe, or the cheese prepared from it, especially goat's milk cheese. In the United Kingdom the consumption of infected cow's milk has, since I started my investigations in 1928, accounted for the great majority of cases, as TABLE 2 shows.

TABLE 2

EVIDENCE OF INFECTION FROM MILK IN 1,032 CASES

RAW MILK OR CREAM DRUNK	CONTAGIOUS ABORTION REPORTED PRESENT	MILK WHEY AGGLUTINATION OR RING TEST POSITIVE	*Brucella* GROWN FROM MILK OR CREAM	COW'S BLOOD SERUM AGGLUTINATED *Brucella*	*Brucella* GROWN FROM COW'S BLOOD
1,032[1]	261	59	61	22	2

[1] This number includes 124 cases in which tuberculin-tested milk alone was drunk. 147 of these 1,032 patients had also had contact with infected animals.

It will be seen that in 1,032 cases (82 per cent. of the 1,255 cases for which the information is available) raw milk or cream had been consumed and after deducting 147 cases in which there had been *actual or possible* contact *with infected animals or their excreta etc.*, there remained 885 in which the consumption of infected cow's milk or cream was almost certainly the source of infection, and in 124 of these cases the milk consumed was from tuberculin-tested herds.

That infection can occur even when small quantities of infected milk have been consumed is shown by the fact that in some of my cases raw milk appears to have been consumed *on a single occasion* only, sometimes in tea, and that a great many of my patients who *have had no contact with infected animals or their products* asserted that they had drunk only pasteurised milk.

Infection by milk containing the *melitensis* or *suis* variety of the organism appears to be easy, as was shown by the work of the

Mediterranean Fever Commission and by Otero [278], but this does not seem to hold for the *abortus* variety.

[illegible]

as is shown in TABLE 3 for my series of cases? [1]

TABLE 3

FAMILY INFECTIONS

RELATIONSHIP OF PATIENTS	INTERVAL BETWEEN ONSETS OF DISEASE	MILK SUPPLY
Daughter Father	18 months	Same in both cases
Father Son	3 weeks	Same in both cases. Good evidence of contagious abortion in herd
Wife Husband	2 days	Same in both cases — raw (tuberculin tested)
Brother Sister	11 months	No information
Husband Wife	Ill at same time	No information
Nephew Aunt	14 months	Same in both cases—raw (tuberculin-tested)
Husband Wife	7 weeks	Same in both cases—husband's own herd. Abortion in herd
Brother Brother Brother	Simultaneous 5 days	All three on same milk supply, agglutination positive
Father Son	8 weeks	Same milk supply—son's herd, with which father had no direct contact.

Apart from family infections there have, in my series, been only eight groups of cases each attributable to an individual milk supply, four of these groups consisting of four cases each, two of three cases

[illegible]

each, and two of two cases. Of the four milk-borne epidemics of this disease reported in the literature the most striking is that of twenty-eight cases in a small town in Maryland, U.S.A., reported by Steele and Hastings [344].

The reason why more than one case on an infected supply is so seldom detected is still unknown. Garrod [137] showed that *Brucella* is more easily killed by hydrochloric acid than any of the other common pathogenic organisms, which suggested that the period of vague ill-health which often precedes the onset of fever gave rise to a hypochlorhydria in the stomach, so leaving the citadel open to attack. Spink and Hall, however, failed to find any raised incidence of achlorhydria in patients with brucellosis Spink [333], moreover, adduces evidence to suggest that dilution of the organism in the milk, and the protection of the tonsillar tissues are more important factors in preventing infection by this means. In one of my cases [No 618], a doctor and a raw milk drinker, the patient had been taking dilute hydrochloric acid for indigestion for the three weeks preceding the onset of the disease. Otero [278], from experiments with human volunteers, found that it was difficult to produce infection by feeding cultures of *Br. abortus* and that the abraded skin was an easier portal of entry for the organisms.

It seems likely, then, that the general resistance of the body to *Brucella*, even in the absence of detectable specific antibodies, is usually high, though so little is known at present about immunity, especially non-specific immunity, that the mechanism involved is quite obscure.

One of my cases illustrates vividly the fluctuations which may occur in the liability of an individual to infection, due either to variations in concentration of the organisms, or lowering of local or general resistance When seeing a girl, aged 9, suffering from undulant fever I warned the father, a doctor, that the source of infection was almost certainly the family's supply of raw milk and I strongly advised him to change to a pasteurised supply. Eighteen months later the doctor also contracted the disease and I found that though he had put his family on a pasteurised supply, he himself had continued to drink the raw milk, which had infected his daughter, because he liked its taste!

[illegible] the disease seems to have been precipitated by [illegible] one case varicella [No [illegible]

CREAM

The cream of an infected milk is usually more heavily infected than the rest of the milk, as the fat globules rising to the surface carry the organisms with them In taking the history of a patient's illness the consumption of cream, and not only of milk, should be enquired into.

BUTTER

Butter rarely contains viable *Brucella*, as 'farm butter' is usually made from milk which has been well soured first and lactic acid easily kills the organism, and creamery butter is always made from pasteurised milk. Butter is probably, therefore, negligible as a source of infection (Lerche [218], Fulton [132]).

ICE-CREAM

Though *Br. abortus* has been recovered from ice-cream made from naturally infected milk, in which it can survive for a long time (Fitch and Bishop [120], Thompson [353]), yet it must be remembered that most ice-cream is made from pasteurised milk and I know of no case of undulant fever in which infected ice-cream has been shown to be the cause of the disease.

CHEESE

Cheese is only a source of infection when it is freshly made and when the milk from which it is prepared has not been efficiently heat treated Matured (fermented) cheeses are always safe (Lerche [218], Carneu and Lafenêtre [54], Taylor *et al* [352]), though little information is available as to the time of ageing necessary to ensure safety Unfortunately freshly prepared cheeses produced from unheated milk are consumed in many parts of the world and they constitute an important source of infection for the populations concerned (Castañeda *et al* [65], Molinelli *et al* [259], Chassagne and Gaignoux [68], Gilman and Marquardt [142], Durante [106])

WATER

As has been mentioned [p 33] Horrocks [173] showed, in 1905, that *Br. melitensis* could survive in sterile tap water for thirty-seven days and Shaw [323] found that it could survive in this medium for fifty days and in unsterile tap water for seventy-two days. Similar, but more detailed, investigations were reported by Poltev and Karkadinovskaya [289] But as regards proof of actual infection by water, inconclusive evidence has been adduced by Chassagne

and Gaignoux [68] and by Julien [201], and Newitt, Koppa and Gudakunst [270] reported an outbreak at Michigan State College in which strong circumstantial evidence pointed to water-borne infection in very exceptional circumstances, but Huddleson and Munger [180] considered that the proof was insufficient, and I agree

FOOD CONTAMINATION

It is difficult to deny the possibility of transmission through the contamination of food by excreta, dust etc, especially in countries in which the human population live in intimate contact with the domestic species which harbour *Brucella*, particularly goats. But those habits will, themselves, make it almost impossible to determine whether infection was the result of ingestion of contaminated food, or of drinking infected milk, eating fresh cheese, handling manure, etc.

DIRECT OR INDIRECT CONTACT

Infection from infected animals and their products may occur through the skin, conjunctiva, or respiratory tract (apart from the alimentary tract, which I have just considered)

OCCUPATIONAL INFECTION

It will be seen from TABLE 4 that though a large number of patients in my series had been specially exposed to infection by direct contact on account of their occupations, yet in the great majority of cases they had also drunk raw milk, so that in only a few cases (e g 18 per cent of the farmers and farm workers) could infection be attributed with some certainty to their occupation.

These and other occupational infections will now be considered in more detail.

LABORATORY INFECTIONS

I have come across a number of cases infected in the laboratory, but these have been excluded from my series as being of artificial origin and therefore not epidemiologically comparable Laboratory infections are, however, so common that it has been said that anyone working for any considerable time with cultures of *Brucella* is bound to become infected The *melitensis* and *suis* species are usually considered to be far more dangerous than *abortus* in this respect (Meyer and Eddie [254], Spink [333]), but a comprehensive survey

of the incidence of laboratory infections in the United States of America, carried out in 1950 [293], giving a total of 1,334 cases, showed that in that country all three species of *Brucella* were about equally involved. The same report concludes, contrary to most previous statements, that such infection, when resulting from handling large quantities of material, is not due to breaks in bacteriological technique, but rather to the fact that the manipulation of such volumes causes a greater amount to be released into the

TABLE 4

OCCUPATIONAL INFECTION

OCCUPATION	NO OF PERSONS	NO DRINKING RAW MILK
Males		
Farmer, farm worker, etc	161	132
Veterinary surgeon or veterinary student	23	13
Butcher or slaughterman	10	5
Living on farm but not engaged in farm work	3	2
Labourer in cattle market	1	1
Labourer in fat factory	1	0
Knacker	1	1
Artificial inseminator	1	1
Females		
Farmer's wife	24	24
Land girl or land worker	4	3
Milk maid	2	1
Living on farm but not engaged in farm work	4	4
Butcher (W A A F)	1	1
Total	236	188

environment Certain pieces of apparatus, such as tissue blenders and shaking machines, which may be employed without any considerable danger in working with other organisms, are likely to constitute a source of infection in the case of undulant fever and tularaemia As to the route of infection, though this has been known to be through the conjunctiva and by accidental ingestion while pipetting a culture, it seems probable that the more usual method is by inhalation of infected droplets or dust (Spink [330], Green [146], Molinelli [257], Meyer and Eddie [254])

VETERINARIANS

Veterinarians are especially exposed to *Brucella* infection and many cases have been reported among them. In my series there were twenty-two veterinary surgeons (of whom one was also a farmer) and one veterinary student. In view, however, of the very special risks of infection from such procedures as the delivery of the foetus and placenta, it is surprising that more veterinarians are not reported as clinical cases of undulant fever Thus Wilson [372] on testing the blood of ninety-eight veterinarians for agglutinins to *Brucella* found the test positive to a titre of one in twenty or over in only fifteen out of sixty-three who had come into close contact with infected cattle or had been engaged in milk inspection; whilst of thirty-five who had not been so exposed the blood serum of only one agglutinated the organism (to a titre of one in forty)

Again Thomsen [356] in a survey of undulant fever in veterinarians in Denmark found only seventeen such cases in the period 1931-5 and two of these were doubtful. All the cases were in young practitioners, usually occurring within a few months of starting practice and *Thomsen considers that older veterinarians may be* [illegible]

in veterinarians are required, as Hofmann [172], in a careful study of Swiss veterinarians, found that 80 per cent. of those engaged in large animal practice contracted the disease.

It may well be that veterinarians usually suffer from only a mild illness which they regard as part of the day's work, or, on the other hand, that they acquire immunity early from small doses and maintain it by constant stimulation of their immune mechanism.

It has long been known that veterinarians are very liable to develop a skin rash on the hands and arms as a result of contact with infected material and the relation of this rash to actual infection is a problem of special interest, not only as regards this particular disease but also because of the light it may throw on the general question of infection and immunity [85].

Haxthausen and Thomsen [165] came to the conclusion that this rash was allergic in nature and they showed that an identical lesion could be produced by the inunction of a *Brucella* antigen 'Abortin', *controls who had not previously been sensitised giving (with very*

few exceptions) negative results. They note, however, that such inunction, though producing the characteristic rash, did not give rise to fever or any general symptoms, suggesting that where such symptoms accompany a naturally acquired rash the patient harbours *Brucella* in his body. (The veterinary surgeon who developed a fever within twenty-four hours of an accidental injection of S 19 vaccine may well have been an instance of the same kind.) One of my cases [No 1107] was a veterinarian who for three years was constantly exposed to infection handling infected cattle, but never developed an arm rash; yet the infection he acquired ultimately was either from handling such cattle or, possibly, from the use of S 19 live vaccine

Mention must finally be made of a special risk of accidental infection peculiar to veterinarians, namely that connected with the vaccination of cattle with *Br abortus* S 19 It has happened on many occasions when using this vaccine to immunise cattle that a sudden movement of the animal has resulted in the needle entering the hand or fingers of the operator, but in cases described by Gilman [141] and by Spink and Thompson [341] the vaccine was squirted into the eye. The consequences have ranged from mild local inflammation to an acute febrile illness, occasionally severe [72]

Thus though S 19 is considered to be of low virulence and therefore not transmissible from bovines to man, it has occasionally produced severe illness when injected accidentally Three of my cases were apparently infected in this way The first was a farm worker, assisting the veterinary surgeon, who received an accidental injection into his finger and a week later developed a fever lasting six weeks The other two patients were both veterinarians, the injections being into a finger and a thumb respectively One developed a fever within twenty-four hours which lasted only four days, whilst the other became febrile forty-eight hours after the injection and was ill for 11 months The former of these veterinary surgeons may well have had an allergic reaction rather than a true infection Unfortunately the organism was not recovered for typing in any of these three cases

Spink [332] has concluded from an examination of the endotoxins of all the *Brucella* species, including S 19, that if the latter could survive and multiply in the tissues the endotoxin produced could cause a serious illness

Though reported infections in veterinarians have almost always

been contracted through the skin or conjunctiva, infection by inhalation of infected dust is an obvious possibility.

FARMERS, SHEPHERDS, GOATHERDS, ETC.

Infections in these occupations are to be expected and the literature is full of them. Though the frequency of disease in any such occupation varies directly with the degree of exposure (intensity and number of exposures) and the *Brucella* species concerned, yet infection can result from a single exposure, as in the case of the mason, described by Loffler [223] who sustained an abrasion working in a stall which had harboured an infected cow

The greatly increased risk of infection to which those persons are exposed whose work brings them into close contact with infected animals is shown by reports from Germany [271, 384], Japan [5], New Zealand [228], Kenya [381], U.S.A. [88, 331, 343], Denmark [354], Romania [290], France [53, 68, 215, 360], Argentina [327], Poland [359], U.S S R , Bulgaria, Czechoslovakia, Hungary, Spain, Sweden, Australia, etc , and in the last nine of these countries [183] workers contracting the disease as the result of their occupations are entitled to compensation.

As with veterinarians, persons in these other occupations are probably most often infected through the abraded skin, but infection from inhalation of infected dust or per conjunctivam cannot be excluded The conditions to which the owners of infected animals are often exposed have been well described by Grand (quoted by Carrère and Renoux [53]) 'nevertheless it is a fact that whole villages in the Ardèche are infected, and there are no end of houses sheltering goats which abort repeatedly on the ground floor, whilst above the owners of the animals, who have been bedridden for weeks, are in the grip of undulant fever'.

Such close contact is not found in the United Kingdom, though many of these occupational infections occur there In my series 236 patients (15·7 per cent.) belonged to this category, but in 188 of these cases infected milk or milk products had probably been consumed, leaving forty-eight (or 3·4 per cent of the 1,421 patients whose occupation is known) in which the infection was almost certainly occupational

BUTCHERS, SLAUGHTER MEN, PACKING HOUSE WORKERS, ETC

This group is also exposed to special risks and infections are common In my series only twelve patients (0 8 per cent) belonged

to this group, but high rates have been reported in other countries, especially where *Br. suis* is involved. Thus Steele [343] found that of the cases in Indiana 15 per cent worked in slaughterhouses and another 30 per cent. in fertiliser (rendering) plants Again Sordelli and Molinelli [327] reported that in the district of Argentina in which the great stock breeding establishments and abattoirs are situated, 90 per cent. of the patients are cases of occupational infection. Spink [333] found that of 244 cases of brucellosis studied in the University of Minnesota's clinics between 1937 and 1954, 134 (54 8 per cent) were employees of meat packing plants and of the thirteen cases out of the whole number which were due to *Br suis*, eleven were such employees. It is interesting to note, however, that 121 of these cases were infected with *Br abortus*, of which fifty-one were in the packing plant employees An analysis of the work done by each of the infected employees showed that those workers coming into direct contact with the freshly killed animals or their viscera had the highest rate of infection A number of the patients, however, had had very casual contact with the infected materials, such as an executive who had merely visited various contaminated areas of a plant The possibility of infection from eating uncooked meat in such plants has already been mentioned [p 35], but I think this must be a very rare source of infection

INTER-HUMAN INFECTION

Inter-human infection is such a common occurrence in most infectious diseases that the paucity of evidence for its occurrence in undulant fever comes as a surprise on first study of this disease Among the hundreds of thousands of persons, such as doctors, nurses, ward orderlies, etc, attending on patients since undulant fever was first recognised as a separate disease there is no evidence whatever of infection from a patient This is all the more remarkable when it is considered how often *Br melitensis* can be grown from the urine of acute cases, and how long it can survive on clothing (p 33) The possibility of infection through coitus was examined by the Mediterranean Fever Commission [250] who isolated *Brucella* from the milk of two women and a vaginal swab from one of them, and also recovered it on two occasions from vaginal swabs of another convalescent woman, and from the cervical mucus of two out of 134 prostitutes in Malta, forty-one of whom showed evidence (sometimes inconclusive) of *Br melitensis* infection Experimental

infection of monkeys via the glans penis was also effected Infection by coitus or by other direct contact has been alleged by many authors [68, 73, 106, 259, 261, 321, 352, 360], but always, in my opinion, on quite insufficient evidence, sometimes amounting merely to the failure to discover any alternative source of infection and every experienced worker in this disease knows only too well how unreliable the evidence of patients is in this respect.

It is remarkable how rare is the occurrence of more than one case in the same family in spite of the fact that a common milk supply can usually be established. The evidence in regard to such occurrences in my cases is shown in TABLE 3 [p. 37]

It will be seen from that Table that in all the instances in which the necessary information was available, the milk supply of the members of each group was the same.

Although, therefore, the possibility of inter-human infection by *Brucella* is impossible to deny, convincing evidence of such an occurrence would seem to be wanting. There is, however, one exception (apart from transfusion) As I have already remarked, Eyre, McNaught, Kennedy and Zammit [117] grew the organism from the breast milk of a convalescent woman in 1905 and Renoux [303], forty-seven years later, reported a case in which he was satisfied that a 5-month-old baby was infected by its mother's milk.

Before leaving this subject a brief reference must be made to the possibility of *Brucella* infection being conveyed from man to man by droplets. Bronchitis and pneumonia due to *Brucella* are not infrequent [p 81] and Lisbonne, Janbon, Roman and Quatrefages [222] isolated *Br melitensis* from the sputum of three patients by guinea-pig inoculation, whilst Meyer and Eddie [255] grew *Br. suis* from mice injected intranasally with the sputum of a negro patient. Dudley [105] reviewing an outbreak of respiratory disease in H.M.S *St Jean d'Acre*, about the year 1860, suggested that the organism concerned was *Br. melitensis* and that infection had been spread by droplets, but his arguments, though of great interest, are unconvincing

TRANSFUSION

A special variety of inter-human infection is transmission by blood transfusion Though the risk of transmitting *Brucella* infection in this manner might appear to be slight, in view of the probably low

concentration of organisms in the blood and the habitual success of the body in dealing with such concentrations, yet Alvarez and Brito [1] reported two cases of such transmission in children with pre-operative negative agglutination tests becoming positive, culture of *Br. abortus* from the blood, and subsequent culture of the same organism from the donor's blood (same donor in both cases) Wood [380] also reported a case in which the donor subsequently became ill and was found to have a high blood agglutination titre

That *Brucella* of all species can survive for as long as six months [illegible]

though small, is quite definite and all blood from donors, except for direct transfusion in an emergency, should be examined for the presence of *Brucella* before being used.

5

THE FATE OF BRUCELLA IN THE HUMAN BODY

WHAT happens to the *Brucella* organisms that gain access to the interior of a human patient? Whether they enter by the skin or by the nasopharynx, they do not usually persist long at the point of entry but pass rapidly to the nearest lymph node, where they are either destroyed by the natural defences or multiply and invade the blood stream. From the blood secondary localisation occurs in the reticulo-endothelial system, especially the spleen, liver, bone marrow, lymph nodes and kidneys, but also at times in the gall bladder. At these sites the organisms secure an intracellular lodging.

The intracellular localisation of *Brucella* deserves more than passing mention as to it are due many of the clinical manifestations of undulant fever and also the difficulties of treatment [322]. As Castañeda [56] has pointed out, *Brucella* is not a true intracellular parasite as it possesses its own enzyme system, which enables it to use rather ordinary material for its metabolism. All the same the intracellular habits of *Brucella* have been demonstrated, both clinically and experimentally, by many workers, in fact Castañeda found that guinea-pigs, rabbits, and mice experimentally infected showed very few extracellular brucellae. The cells invaded are phagocytes, mostly mononuclear, which seem to deal with the invaders less effectively than the polymorphonuclear cells [129a, 172a], as a reduction in the latter is often associated with persistence of in- [illegible]

Castañeda suggests, or whether they are dealt with more efficiently in their new situation, as Miles thinks, is unknown. In any case proliferation inside the cell reaches its maximum about the fifth day, when the cells are destroyed and the organisms once more exposed to phagocytosis and to the humoral defences. The extracellular fluids do not appear to be favourable for the multiplication of *Brucella*, except where heavy tissue destruction provides a rich pabulum.

The granulomata so frequently seen in brucella infected tissues and often quite indistinguishable from tuberculomata [FIG 10], are mostly composed of epithelioid cells, with or without giant cells of the Langhans or foreign body types, as well as lymphocytes, plasma cells and occasionally eosinophils [330] These granulomata appear to be the result of a reaction round a wandering macrophage or locally parasitised cells, which are surrounded first by monocytes



FIG 10 *Brucella* granuloma in a biopsy specimen from the liver of a chronic case

(and perhaps polymorphonuclears) and then walled in by lymphocytes Abscess formation or caseation may be the end result of these reactions [56] Two of the most striking lesions due to *Brucella* are those in the heart and the bones In my series there were five cases of *Brucella* endocarditis and all these cases were fatal [TABLE 16, p 154], as were also three cases in Spink's [333] series of 244 (his only fatal cases) Hughes [181] had four cases of 'organic disease', which was not known to be present before the onset of pyrexia, and these cases, which were all fatal, were probably cases of *Brucella* endocarditis

Bone lesions of *Brucella* origin are far commoner but will be considered later [p 72]

As regards the liver, the basic lesions are granulomata in the lobules and portal spaces with a cellular infiltrate in the portal areas and sometimes degeneration of parenchymal cells and focal necrosis [108, 338]. The granulomata are indistinguishable from sarcoidosis, and sometimes from the lesions of tuberculosis and syphilis. Enlargement of the organ often results *Brucella* infection can also produce cirrhosis of the liver [247, 331] and diabetes [217] Abscess formation and subsequent calcification may also occur in the liver and the spleen [333*a*]

Granulomata are also common in the bone marrow and in the spleen. In the latter organ enlargement follows invasion more often than is the case for the liver, and this is seen to be associated with a marked increase of cellular activity, hyperplasia of the reticulum rather than of connective tissue, and congestion with multiplication of the invaders. Castañeda [56] suggests that the specially profuse growth of *Brucella* in the spleen is due to the presence there of cells especially favourable for such intracellular growth. It might be supposed that the spleen was specially equipped for dealing with *Brucella*, but experiments with splenectomised and normal mice do not seem to support this [35]

Brucella can often be recovered from the sternal marrow when blood culture has failed, and although it is often difficult to recover it from patients who have been treated with antibiotics some weeks previously [156], yet the organism can survive in marrow for many years, presumably in caseated granulomata, without giving any indication of its presence and then suddenly burst into activity [p. 53].

DEFENSIVE ACTION OF THE BODY

HUMORAL

Brucella, in common with other Gram-negative organisms, is destroyed in the blood by the action of antibody in the presence of complement, and this is not dependent on the presence of phagocytes [155] Curiously enough there is a species difference here, as Hall found that whereas *Br. abortus* was easily killed by normal human serum, *Br suis* and *Br melitensis* were resistant to its action [153] Another curious complication of this picture is that the serum in chronic cases loses a good deal of its bacteriolytic power, which is restored when such serum is diluted Hall believes this 'inhibition prozone' effect to be due to the stimulation of a specific inhibitor, preventing the normal antibody-complement lethal action on

Brucella Agglutinating antibodies assist phagocytosis by promoting clumping of the organisms.

CELLULAR

There seems no doubt that the mononuclear cells of the blood are the most formidable antagonists met by the invaders and a lymphocytosis was present in nearly three-quarters of my cases, being absolute in more than a third [TABLE 8, p. 77], but the polymorphonuclear leucocytes, which were increased in more than half my cases [TABLE 9, p. 78], probably play some part in localising the infection In the fixed tissues, as we have seen, the macrophages play an important part along with the phagocytic cells of the spleen and liver. The macrophage attack is intensified as the result of previous infection [274, 299], and in man deliberate reinfection soon after recovery from undulant fever has been shown, in at least two cases, to produce local inflammation and adenitis, but very little systemic disturbance [43, 258]

HYPERSENSITIVITY

This reaction to infection is particularly common in undulant fever and its clinical aspects will be considered later [p 92] The mechanism of the hypersensitivity reactions is only partially known and the phenomenon can only be completely produced by actual infection [pp 42, 43] Such hypersensitivity can persist indefinitely if untreated Its only advantage to the host seems to consist in its tendency to localise the infection

IMMUNITY

Though, as we have seen, some considerable degree of immunity has been demonstrated as occurring soon after the termination of an attack of undulant fever, the duration of such immunity is not easy to determine owing to the frequency of relapses and the great difficulty of distinguishing between these and fresh infections, especially when patients are constantly exposed to infection in their occupations There seems little doubt that second attacks do occur, especially when patients who have apparently recovered are exposed [illegible]

evidence of a recurrence of this disease due to *exogenous reinfection*; cases claimed as reinfections seeming to be, in fact, very belated relapses. Hughes [181], examining the medical histories of *many thousands of soldiers serving in the Mediterranean, found only one case in which there may have been a true second infection, after an* interval of twenty-four years, and this case was not proved.

This difficulty was brought home to me by the first case of this disease which I ever saw, a lady who, to the best of my belief, *contracted the disease in England in 1886* and had it without intermission until 1911, when she had an interval of three years' freedom. In 1914 the disease recurred, with exactly the same symptoms as previously (daily drenching sweats, headaches, lassitude, depression, constipation, insomnia, etc.), the recurrence following the consumption of raw sheep's milk cheese in Switzerland and lasting until 1933 when she lost all her symptoms and was still free of them in 1936. Was this a reinfection or a relapse? Relapses can apparently occur after much longer intervals than three years [p 53] Olin [274] reported the case of seven laboratory workers who worked continuously with *Brucella* for a long time and afterwards were exposed to heavy infection. They remained well, but developed marked skin sensitivity He also found that four persons who had had undulant fever from one to six and a half years previously showed increased phagocytic activity, as did also seven out of ten bacteriologists who had worked with *Brucella* cultures and gave a positive intradermal test. On the other hand two bacteriologists and seven other persons who had not worked with *Brucella* cultures showed little or no phagocytic activity. Molinelli [258] suggests that the existence of immunity is indicated by hyperallergy (i e. a marked intradermal reaction) and a strong opsono-cytophagic reaction of [illegible] bacteriologist [illegible]

develop undulant fever but only a marked allergic reaction.

Burnet [43] showed in 1925 that experimental reinfection of guinea-pigs with *Br melitensis* was very difficult and that such attempts provoke a typical Koch phenomenon. He also showed that these attempts during the active disease did not increase its severity.

Finally it is important to remember that the constitution of the host has a profound influence on immunity, whether natural or acquired [172a], and, as Meyer [253] has put it, 'resistance of any

animal to a great many infections is a compound of its genetic constitution'.

BACTERAEMIA

The previous account may have given the impression that bacteraemia is a fleeting phase in this disease, but that this cannot be true is shown by the frequency with which, in the United States of America at any rate, the organism can be grown from the blood. Moreover, the most acute and serious symptoms of the disease are evident at those times when blood culture is most easily accomplished, such as at the height of the pyrexia, suggesting a correlation between bacteraemia and the severity of the symptoms In my experience negative blood culture can sometimes be turned into positive by producing a marked general reaction with fever by injection of a foreign protein [p 129]

At the same time the ending of bacteraemia, whether occurring naturally or as the result of chemotherapy, does not necessarily mean the recovery of the patient

The *Brucella* endotoxins liberated by destruction of the organisms whether in the blood stream or in the cells of the fixed tissues, have an effect not only on the body in general, but also on the white blood corpuscles, changing their numbers, both absolute and relative [pp 77, 78]

SURVIVAL OF BRUCELLA

One of the most remarkable features of *Brucella* infection is the frequency with which the organisms persist in the body for long periods, often without giving rise to any symptoms Smouldering illness from this cause will be considered later [p 109], but a word must be said here about symptomless survival Proof of such survival is obtained when a local injury leads to a recurrence of the disease in all its former features, after a symptomless interval, and the recovery of the same species of *Brucella* from the blood, an abscess, etc A good example is the case, which I have often quoted, reported to me by Professor Debono of Malta The patient was a man who as a young officer in Malta had contracted *Br melitensis* infection from goat's milk or cheese, but had recovered and had had no recurrence for many years This man had returned to Malta in later life and had, it is believed, taken every precaution to avoid goat's milk and cheese with the memory of his former illness still vivid in

his mind. Then one day, when 80 years of age and in good health, on his usual daily ride he was thrown from his horse and fractured his femur. The bone healed well but fever mysteriously persisted and in the end *Br. melitensis* was grown from his blood. The conclusion that the organism had been lurking in the marrow of his femur for all these years, though not capable of proof, seems to me almost irresistible. A similar case in which a recurrence, following a two years' period free from symptoms, was provoked by the kick of a horse, was observed by Borts [27a].

6

THE INCIDENCE OF UNDULANT FEVER

THOUGH, as we have seen in Chapter 1, the early history of *Brucella* infection in man and animals in different countries is very obscure, it is at any rate clear that undulant fever has, in the last thirty years, been detected in one country after another and the process still continues

GEOGRAPHICAL DISTRIBUTION

THE UNITED KINGDOM

As regards the United Kingdom, reliable statistics of the incidence of undulant fever are not available, as neither this disease nor bovine contagious abortion is compulsorily notifiable However, I have been collecting cases of undulant fever since 1929 with the kind co-operation of medical officers of health, general practitioners, pathologists, veterinarians and others, and though such help steadily increased during the first ten years of my study, yet since the inauguration of the Emergency Public Health Laboratory Service (now the Public Health Laboratory Service) by the Medical Research Council in 1939, my sources of information have remained more or less constant My figures, therefore, probably depict approximately the general changes of incidence year by year [p 122], though the true incidence must be many times greater than that shown in TABLE 5, for reasons which I will give presently

Table 5 shows the effect of my investigations, starting in 1929, also that in spite of the campaign for vaccination of cattle with S 19 vaccine, which was in widespread operation by 1946, the number of cases of undulant fever reported to me annually has shown no sign of falling off The diagnostic criteria on which these cases are based is given on page 99

My reasons for concluding that the true incidence of the disease is much greater than that recorded by me are as follows It was suggested by G S Wilson in 1932 [371] that a rough idea of incidence

could be obtained by taking the annual notifications of typhoid fever and applying the reduction factor given by the relative frequency

TABLE 5

CASES OF UNDULANT FEVER IN MY SERIES (ENGLAND AND WALES) BY YEAR OF INCIDENCE

1914	1	1931	41	1941	59	1951	67
1917	1	1932	66	1942	68	1952	58
1921	1	1933	63	1943	66	1953	77
1923	1	1934	55	1944	73	1954	75
1925	3	1935	43	1945	47	1955	65
1926	2	1936	51	1946	26	1956	40
1927	7	1937	58	1947	24	1957[1]	13
1928	6	1938	43	1948	48		
1929	18	1939	23	1949	66		
1930	33	1940	24	1950	71		

[1] This year should be regarded as incomplete

of agglutination of *Salmonella typhi* and *Br. abortus* by sera submitted for routine Widal reactions This calculation gave an incidence of 400 to 500 cases per annum, but this estimate I believe to be too low for the following reasons.

1 Very mild cases certainly occur in which no agglutination test is done, either because the patient does not consult a doctor or because the doctor is content with a diagnosis such as 'feverish cold' or 'mild influenza'. Moreover, I myself have had three cases, and many other workers have reported other cases, in which fever was absent during most or even the whole of the illness, though *Br. abortus* was grown from the blood

2 Cases occur in which, as was first noted by Bassett-Smith [10] in 1912, the agglutination test remains persistently negative, though *Brucella* is grown from the blood

3 A single negative agglutination test is far too often accepted as definite evidence that the patient is not suffering from undulant fever, though agglutinins take at least five days to develop in the blood and sometimes much longer, and 'prozones' of negative agglutination are common in this disease [pp. 102, 103]

4 Practitioners on their first encounter with this disease have often remarked to me that they have had a number of similar cases in past years which they now thought must also have been cases of undulant fever

5. Cases often have to wait months or even years for a correct diagnosis [p. 109], so that many such cases must be missed altogether.

My cases have been scattered all over the country, every English county and all Welsh counties except Radnorshire and Merioneth being involved.

OTHER COUNTRIES

In the United States about 4,000 cases are reported yearly, but it has been estimated that the true incidence, including that of so-called chronic brucellosis, is probably 40,000 to 100,000 per annum [200].

The true incidence of undulant fever is mostly a matter of speculation, though where animal brucellosis is wiped out it must soon thereafter be negligible. It must suffice here to state that undulant fever has been credibly reported from the following countries:

Aden
Algeria
Argentina
Australia
Basutoland
Bechuanaland
Brazil
British Somaliland
Bulgaria
Canada
China
Colombia
The Belgian Congo
Corsica
Crete
Cuba
Cyprus
Denmark
Egypt
Eritrea
Finland
France
French Equatorial Africa
Germany
Grand Canary
Greece
Hungary
India
Indonesia
Iraq
The Republic of Ireland
Italy
Japan
Kenya
Lebanon
Levant
Malta
Mauritius
Mexico
Mozambique
Netherlands
New Zealand
Nigeria
Northern Ireland
Norway
Nyasaland
Pakistan
Peru
Philippines
Poland
Portugal
Puerto Rico
Romania
Sardinia
Scotland
Sicily
South Africa
Southern Rhodesia
South West Africa
Spain
Sudan
Swaziland
Sweden
Switzerland
Tanganyika
Tripoli
Tunisia
Turkey
Uganda
U.S.A.
U.S.S.R.
Yugoslavia

AGE AND SEX DISTRIBUTION

Marston [246] says 'it affects, *par excellence*, young men, under 35, particularly those of rheumatic diathesis, next in frequency children, most infrequently the aged'. Of 500 non-fatal cases collected by Hughes [181] the average age was 23 (range 16 to 47); whilst of thirty fatal cases recorded in the books of the military hospital at Valetta, he tells us the average age was also 23 (range 19 to 28). Of all the many series reported in the literature since then there is a general agreement as to 20 to 40 being the commonest age at onset, children under 6 years of age being rarely affected and infants very

rarely indeed. Of the 1,459 cases in my series, whose age was definitely known, the age and sex distribution is shown in TABLE 6

TABLE 6

AGE AND SEX DISTRIBUTION

AGE GROUP	0 TO 4	5 TO 9	10 TO 14	15 TO 19	20 TO 24	25 TO 29	30 TO 34	35 TO 39	40 TO 44	45 TO 49	50 TO 54	55 TO 59	60 TO 64	65 AND OVER
Males	8	51	40	62	58	99	115	103	107	92	89	56	35	33
Females	4	19	28	28	32	35	50	53	50	47	45	29	49	42
Total	12	70	68	90	90	134	165	156	157	139	134	85	84	75

As will be seen, only 12 children were under 5 years of age, but there were 150 (10 3 per cent) under 15.

As regards infection in children, Hall's observations [153] are of interest. He showed that although the blood serum of infants three months of age or less was strongly bactericidal for *Br. abortus*, two-thirds of the infants between 4 and 16 months of age whom he examined had serum with little or no bactericidal activity. On the other hand the serum of all children eighteen months old or older, as well as that of normal adults, was strongly bactericidal for *Br. abortus*. He concluded that the protection of young infants was due to passive transfer of antibodies from the mother, but the development of bactericidal powers later in life remains a mystery.

Lovell [227], in an examination of resistance to infection in young animals, including man, has suggested that the failure of the organism to establish itself in children may be due to lack of suitable soil before puberty for the growth of *Brucella* Hagebusch and Frei [152], in a review of the literature up to 1940, suggest that undulant fever is really a common disease of childhood, but being usually self-limiting at this age, spontaneous recovery is common and the real incidence is masked

As regards sex, Hughes [181] says 'sex appears to have little or no influence, any apparent difference being due to age, occupation and surroundings In a given number of married families in the army, the writer has, for these reasons, found the women, if anything, more subject than the men ' His was, of course, a special population, but the remark about the women suggests that in those days, before

the causative organism had been discovered or goat's milk implicated, the women probably drank more infected goat's milk than the men and so ran a greater risk of contracting undulant fever. Nevertheless in most series since reported the men have outnumbered the women by at least two to one [15, 150, 166, 352, 384]

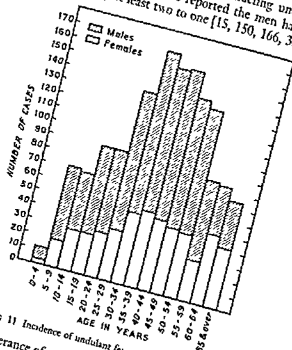


Fig 11 Incidence of undulant fever by age and sex

This preponderance of male patients has been explained by some authors as entirely due to occupation, but it has been shown in France [352], in Romania [290] and again in Turkey [278a], that when both sexes are exposed to infection in the same environment about twice as many males as females contract the disease Again, when occupational cases are excluded the remaining cases still show a preponderance of males over females (Olin [274] more than two to one, Feig [119] three to one) In my series there were 968 males and only 524 females, or among those with no occupational exposure 762 males and 483 females [1] This conclusion has, however,

[1] These figures include 533 cases which are not included in TABLE 6 because their exact ages are not known

not passed unchallenged, as in the series of 268 cases in Minnesota reported by Magoffin *et al.* [241], if we take the two age-groups of the whole series which these authors selected as containing those persons infrequently exposed to direct contact infection, although in the group under 13 years of age there were forty-three males as against only twenty-seven females, yet in the group aged 55 years or over there were only seventy-eight males as against eighty-three females. Again in this series three-quarters of the male patients were in the third, fourth and fifth decades of life, whilst the females showed an almost uniform distribution through all the age groups.

However, in my series [FIG. 11] 60·5 per cent. of the males were in the third, fourth and fifth decades of life, whilst for females these decades contained 52·3 per cent. of the total—a distribution in striking contrast to Magoffin's.

Though the sex incidence of this disease merits further investigation, the weight of evidence seems to me in favour of a greater susceptibility of males to infection (or at any rate active disease) other things being equal, and it may well be, as Taylor *et al.* [352] suggest, that after puberty females are relatively resistant to clinical attacks of undulant fever.

7

CLINICAL FEATURES

INCUBATION PERIOD

THE incubation period in this disease is extremely variable, depending on such factors as the virulence of the infecting strains, the route of infection, including the varying ability of different tissues to combat or delay infection, variations in dosage, etc

A feature of the disease which makes the incubation period particularly difficult to determine is the frequency with which a period of vague ill-health precedes the onset of fever, or at any rate resort to a doctor Thus there may be weeks or months of ill-health followed, often suddenly, by the onset of fever, sweating, headaches, etc, and this prodromal period can be regarded as either predisposing to undulant fever or as the initial phase of the illness In favour of the latter view is the fact that the patients often visit their doctors whilst still at work, complaining simply of being over-tired or 'out of sorts', and are found to have a temperature of 102°F (39° C) or higher [p 63] On the other hand infection by milk, for instance, only after long, continuous exposure to milk known to be infected, suggests that ill-health may often be the determining factor in lowering resistance and so admitting the enemy into the fortress

The determination of the actual period in a particular case is usually only possible where a single exposure is involved, as in laboratory accidents or those connected with vaccination in the field A minimum period can, however, be determined when the patient has changed from an employment involving special risk and subsequently contracts the disease, or a maximum period where, for instance, the patient has changed from a pasteurised to a raw, infected milk supply, as in the epidemic described by Dooley [101] in which the maximum incubation period seems to have been ten days [p 101]

I have already [p 43] mentioned my case of a veterinarian who developed a fever, which has lasted already five and a half years, forty-eight hours after an accidental injection of S 19 vaccine, and if the organism had been isolated and typed this would have been

the shortest, verified incubation period of which I know. Wright [382] and Birt and Lamb [24] had two patients who developed the disease fifteen days and sixteen days respectively after subcutaneous injection Shaw reported infection of a monkey through the conjunctiva in four to ten days and one of my cases was infected by this route in thirty-one days. Otero [278] infected a volunteer through the abraded skin in ten days. Infections by the mouth have had incubation periods as short as six days [12], but often much longer. Though infection by the mouth seems usually to take two to four weeks, I am in agreement with Spink and other authors of experience that several months may elapse between the time of exposure and the appearance of symptoms, both in alimentary and cutaneous infections.

TYPES OF ILLNESS

There can be very few diseases with a greater variety of clinical manifestations than undulant fever The onset may be sudden or so gradual that the patient can give no definite date for it. It may start with a brisk bout of fever or no fever may be detected, not only at the beginning but throughout the course of the disease, as in five of my cases The course of the disease may be continuous, with only slight or temporary remissions, or a mild febrile onset may be followed by weeks, months or years of afebrile illness, often not connected by the patient or his doctor with the original attack. Again the patient may suffer from a succession of febrile episodes with intervals of a few days or weeks in which he may be free of symptoms or only suffer vague ill-health. Lastly, after a definite initial illness, there may supervene a long period of perfect health, suddenly interrupted by a recrudescence of illness [see also p. 110]. Such are the variations in the natural course of this disease, but they can, of course, be greatly modified by chemotherapy which, as we shall see, tends to banish the symptoms though not always the causative organisms.

The natural variations will seem less unaccountable to the reader who has studied the account of the nature of *Brucella* and its fate in the human body set forth in Chapters 2 and 5. Thus when the organism is gaining access to the blood stream, fever and other acute symptoms will appear, whereas when it is shut away in granulomata etc the patient will be symptomless. Between these two extremes will be the occasional release of organisms or their

toxins into the blood stream, producing short, febrile or symptom-full episodes, or the triggering off of the allergic mechanism.

The acute case can start with slight fever, malaise, sweating and headache, passing perhaps as a feverish cold, or be of the fulminating type, commoner with *Br. melitensis* than *Br. abortus* infection, in which there is a sudden onset with high fever, haemorrhages from the lungs or bowel, under the skin, or in the joints, or with severe thoracic or abdominal pain simulating pleurisy or peritonitis [p 83].

With a disease possessing such a rich variety of manifestations clinical classification is difficult, but the following represent the varieties most commonly encountered

Ambulant—Undulant—Moderate continuous or daily remittent—Moderate relapsing—Nervous and toxic—Allergic—Malignant, fulminating and haemorrhagic

AMBULANT

All workers in this field have been struck by the frequency with which patients come to the doctor complaining of increasing fatigue and malaise, which, however, have not made them stop work, and are found to have a temperature of 102°F. or more. This history of a male clerk aged 54, is typical

CASE 981 His doctor reported 'This patient came to me after three weeks illness, during which time he had attended his own doctor three times, but no satisfactory diagnosis had been made and he had continued at his work although feeling far from well He was due to go for his summer holiday next morning and had asked me to see him "just to give him something to buck him up for the long journey" He didn't wish to bother his own doctor about it I thought he looked in remarkably good health but as a matter of habit felt his pulse and was surprised to find him burning hot His temperature was 102 8°F' It is of interest to note that this patient, who was seen in August 1949, and who subsequently developed classical symptoms of this disease, had had similar attacks once or twice a year since 1914!

Such patients usually develop the full-blown disease and are sent to bed, but sometimes they remain ambulant throughout It is from the ranks of these patients that are recruited the cases which some American workers label chronic brucellosis and of which a fuller description will be given later [p 109]

UNDULANT

This is the commonest type of case in England and Wales and in the Mediterranean countries, which is why Hughes called the

disease undulant fever, but apparently it is not a common type in the United States of America [176, 333] In my cases the undulating type of fever often took some time to develop, but of the 319 cases in which a chart covering three weeks or more was available 74 8 per cent. showed typical undulation (as also did many of the shorter cases).

FIG 12 is part of the temperature chart of CASE 114, a typically undulant case in which the fever was undulant from the beginning In spite of the wide temperature excursions this patient, a male of

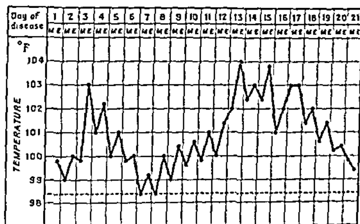


FIG 12 Part of temperature chart of an undulant case.

23, suffered only from heavy sweating, severe headache and some abdominal discomfort, though the fever lasted three months

Chemotherapy may, of course, destroy this pattern if employed early in the disease The daily rise usually occurs in the afternoon and is often detected by a burning feeling of the face and the onset of headache The sudden fall occurs during the night or in the early hours of the morning and is often accompanied by a drenching ... Many patients feel pretty well each day before the onset of ... often ... result ... e case ... parent ... ain by relapse. Malaise, anor- ... and sometimes arthralgia and sore throat, become more pronounced as the disease continues.

They also increase as the undulation reaches its peak, fading away gradually as the line of daily crests declines towards normal

These undulations may be continuous over a long period without a return of the temperature to normal, whilst at other times or in other cases the waves will be interrupted by apyrexial periods of varying length Often towards the end of the illness these intermissions become longer, but it is important to realise that even without any treatment the temperature may drop rather suddenly to normal or sub-normal, when the fever seems in full swing, and either remain there or show one or two isolated waves before it finally settles Rigors are not uncommon in this type of case and even more common in the more serious types of the disease. They occurred in 531 (35.4 per cent.) of my cases

MODERATE CONTINUOUS OR DAILY REMITTENT

In a much smaller proportion of cases regular waves are absent and the temperature curve displays only slight variations over long

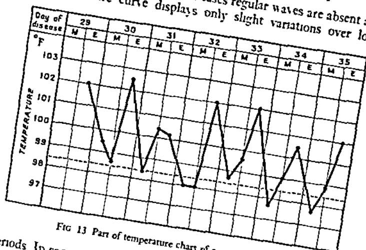


FIG 13 Part of temperature chart of a remittent case

periods In some cases, however, there are considerable fluctuations but with a daily drop to normal or below, or there are peaks similar in appearance to the classical undulations, but differing from them in one essential particular, namely that the low temperatures of each day are all roughly equal and usually below the normal line [FIG 13] Apart from the symptoms already described for the ambulant type of case these patients may suffer from constipation,

anorexia, pains in the limbs, joints or back, or perhaps an occasional mild rigor.

FIG 13 is part of the tempertaure chart of a builder, aged 30, who was first diagnosed as a case of enteric fever:

CASE 46. At the beginning of September this patient began to feel off colour and a week later after playing a game of golf he went to sleep in his chair, but still felt tired on waking That evening he took his temperature and found it was 103·5°F. (39 7° C). He had heavy night sweats This first phase lasted till the third week in September, when he apparently recovered, only to relapse at the beginning of November with a similar attack. He had many rigors (unusual in this type of case) but no other symptoms except headache and tiredness.

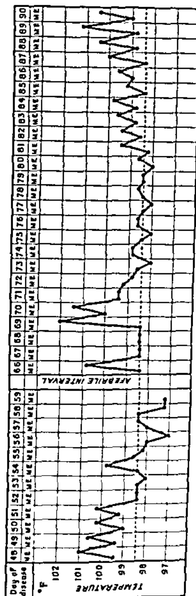


FIG 14 Part of temperature chart of a relapsing case

MODERATE RELAPSING

Many patients have a more irregular type of fever with afebrile intervals of several days or weeks, followed by a moderate exacerbation for a limited period and these alterations may continue for weeks, months or even years [FIG 14] The symptoms are much the same as for the previous category, but even in the afebrile interval these patients are seldom comfortable —a useful point in prognosis [p 153] Enlargement of the spleen and liver are prominent in such cases, as are also arthralgia and arthritis.

In FIG. 14 is shown part of the temperature chart of a typical relapsing case·

CASE 100. The patient, a surgeon of 54, became ill on 18 April and went to bed for four days, when he got up and returned to work but 'felt very rotten' for the next three weeks, getting exhausted after walking a very short distance On 6 May he motored to the coast and crossed to France, where he spent a fortnight visiting the battlefields During this time he felt well during the day time but had rigors in the evening and went to bed directly after dinner each night On 30 May he returned home, but went to bed on 1 June with a fever and next day was admitted to a nursing home, where he stayed till 16 June with malaise and heavy sweating His temperature stayed normal until the evening of 22 June, but during this time he 'still felt like nothing on earth' On the return of fever the symptoms were the same as before, but in addition he had ulcers in the mouth whenever his temperature rose This bout of fever lasted until 29 July, though, as will be seen from the chart, it was around normal from 30 June to 7 July After more travelling abroad he had a return of fever for four days in September and then made a rapid and complete recovery

NERVOUS AND TOXIC

The nervous manifestations of the disease are considered in detail later [pp 88–92] and here it will suffice to draw attention to the type of case in which they are chiefly manifested In such a case there is usually a sudden onset with a brisk fever, but these patients are generally not very seriously ill, their nervous symptoms being attributable rather to toxaemia than to actual invasion of the nervous symptom by *Brucella* Nevertheless there may be such alarming signs and symptoms as delirium, aphasia, and suicidal tendencies, associated with little or no fever In elderly or debilitated patients this degree of toxaemia may be dangerous

The patient whose temperature chart is shown in Fig 15 was a married woman aged 64 Besides malaise, fatigue, headache, anorexia and constipation, during the first two weeks shown on the chart she was at first semi-conscious, then mentally confused and restless and was 'swearing like a trooper', though she was a decent woman in ordinary life In addition she had some oedema at the base of both lungs and her spleen became palpable In spite of the early alarming symptoms fever, as will be seen, was slight and most of the time absent and she made an uninterrupted recovery (Hobbs' case p 90)

MALIGNANT, FULMINATING AND HAEMORRHAGIC

This type, of which Hughes [181] gives a vivid description, is commoner with *Br melitensis* infection, but I have had several such cases, all fatal The onset is usually sudden, with severe headache

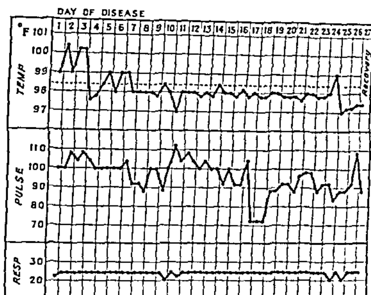


FIG 15 Part of temperature, pulse and respiration chart of a toxic case

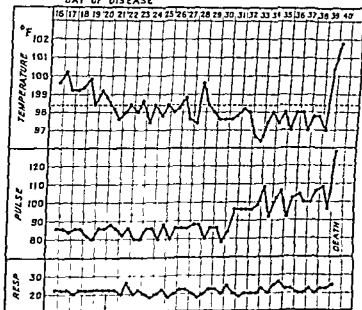


FIG 16 Part of temperature, pulse and respiration chart of a malignant case

and pains all over the body. The face is flushed, the tongue swollen and heavily furred and the breath often very offensive. Abdominal tenderness, especially over the spleen or gall bladder, is common, often accompanied by nausea or vomiting, thirst and anorexia. In spite of the severity of the symptoms the temperature is not usually very high, even in fatal cases

CASE 920 FIG. 16 represents the last portion of the temperature chart of a retired clergyman aged 86, and it illustrates the moderate fever referred to above and the terminal spike, to which Hughes called attention This patient's most marked manifestations were exhaustion, pains in the back, limbs and joints, heavy sweating and marked anorexia Sometimes the lungs are involved, as in CASE 638, a farmer's wife, aged 39, whose fever lasted 26 weeks before its fatal termination In this case vomiting, tenderness over the gall bladder, and visual disturbances—('spots floating')—were the outstanding features After two months she developed an empyema, though all efforts to grow *Brucella* from the fluid were unsuccessful Towards the end a pleuro-pericardial rub developed behind the left superior portion of the sternum

SIGNS AND SYMPTOMS

Of the 304 different signs and symptoms recorded in my cases the frequency of the commonest ones is shown in FIG 17

This gives a general idea of the sort of case in which a diagnosis of undulant fever should be considered, but it is important also to note the signs and symptoms which are less often encountered, especially as some of these are apt to suggest diagnoses leading to unpleasant diagnostic and therapeutic procedures, as will be seen presently It will be convenient, therefore, to consider the clinical manifestations of the disease by systems

SKIN

The commonest of all symptoms is *sweating*, which varies from the moderate sweats common to many fevers to the drenching, sour-smelling sweats which told the old physicians that a case of undulant fever was in a ward the moment they entered it Thus CASE 1, a female who probably contracted the disease in 1886, was still having daily, drenching sweats when I saw her first in 1929—sweats which soaked through her clothes in a few minutes and had prevented her accepting late afternoon or evening invitations during nearly all those years In most cases, as in this one, the sweats occur in the afternoon or evening when the temperature falls suddenly, often

Sign or symptom	Cases
Sweating	1180
Weakness	1141
Malaise	1077
Headache	972
Anorexia	902
*Pain	822
Constipation	589
Rigors	531
Spleen Enlarged	333
Cough	326
Sore Throat	258
Arthralgia	208
Abdominal Tenderness	182
Rash	126
Epistaxis	125
Abdominal Pain	114
Liver Enlarged	90
Vomiting	82
Diarrhoea	81
Visual Disturbances	81
Adenitis	68
Depression	50
Insomnia	41
Arthritis	40
Tenderness over Gallbladder	40
Loss of Weight	38
Bronchitis	32
Buccal Ulcers	22
Melaena	22
Irritability	21
Somnolence	18
Photophobia	17
Orchitis	17
Haemoptysis	14

* Other than headache, arthralgia, or abdominal pain.

FIG 17. Most frequent signs and symptoms in 1,500 cases in England and Wales.

3 or sometimes 6 or 7 degrees Fahrenheit within an hour (3 F = 1 7 C) The characteristic sour smell of the sweat is commoner in *Br melitensis* than in *Br. abortus* infections.

Skin *rashes* of various kinds have been described by many authors [55, 81, 83, 118, 165, 221, 263, 269] Those which occurred in 126 of my cases were of many varieties, the commonest being *erythematous* (15 cases), and a *roseolar rash* (14 cases) closely resembling the classical 'rose spots' of enteric fever.[1]

A *papular rash* was present in twelve cases and other varieties were macular (9), purpuric (7), urticarial (7), morbilliform (5), petechial (5), scarlatiniform (4), rubelliform (2), vesicular (2), maculo-papular (2), sudaminal (2), and prurigenous, seborrheic, 'butterfly', pustular, and acneiform (1 each)

In twenty-eight cases the rash, which was usually fleeting, was not seen by me and the description given was insufficient for classification Spink [333] also had a case with a butterfly rash

light red, irregular blotches appeared on the arm, which on closer inspection seemed to consist of adjoining raised points. This erythema disappeared on firm pressure and in any case faded in

mm in elevation This type of rash lasted for three or four weeks and occasionally there was necrosis, sloughing and scarring Both types were accompanied by intense itching or burning It is interesting to note that similar rashes occur in some cases of undulant fever in which there has been no contact of the skin with infected material, as in three Swiss cases described by Custer [81][2]

Herpes simplex or *labialis* was present in five of my cases *Erythema nodosum* has been reported and was present in one of my cases That this manifestation is not always accidental is shown by the case in which Castañeda [55] obtained *Brucella* from the lesions by scraping The same author had ten cases of *purpura haemorrhagica* in a series of 370 cases, a much higher proportion than in the

experience of Hughes, who had only two cases in all, though reports by various Italian authors suggest that it may be a commoner occurrence now in the Mediterranean area. Pigmentation of the skin was common in Castañeda's cases and my CASE 1530 had a golden-brown pigmentation of the forehead and temples In this case, as in Castañeda's, the asthenia was marked, suggesting that the suprarenal glands may have been affected Temporary loss of hair was common in Hughes' prolonged cases. It occurred in two of my cases, in which the fever lasted eleven weeks and sixteen weeks respectively

MUSCLES, BONES AND JOINTS

Pain in the back and limbs is very common in this disease (54·8 per cent. of my cases) and most of it is of the aching variety common to all febrile diseases. Sometimes, however, it is the result of a local lesion and it is important to bear such a possibility in mind

Arthralgia was present in my series in 208 cases (13·9 per cent), but in forty-one cases definite *arthritis* or peri-arthritis was present, more than one joint being involved in twenty-one of these cases There was usually redness, swelling, and tenderness round the joint, with pain on movement and sometimes definite *effusion* into the joint Arthritis is commoner in *Br. melitensis* infections [Baker, 6] than in those due to *Br abortus* and arthritis with effusion appeared in some 40 per cent of Hughes' cases

Brucella spondylitis, in my opinion, deserves more attention in this country than it receives In Spink's experience [333] it was one of the most frequent complications of undulant fever, and FIG. 18 shows the characteristic local proliferation, or parrot's beak, in one of his cases with the further proliferation and fusion of the vertebral bodies a year later

Whilst the lumbar spine is most often affected (eight out of fourteen of Spink's cases), *the cervical and thoracic spine may also be involved*, and Janbon [188] and his co-workers have shown that pain in the neck, so common in undulant fever, may often have this *origin, in fact they have the impression that in undulant fever all* symptoms in the joints, whether mobile or fixed, originate in the *bones, even when the X-ray examination shows a normal appear*-ance [188] Roger [310] says that *Brucella* spondylitis of sacro-iliac

tina and Molinelli describes three types ...



Fig 18 *Brucella* spondylitis, showing parrot's beak proliferation of lumbar spine.

osteomyelitic, and arthritic, but these forms may appear simultaneously or successively. Often the changes are localised in the intervertebral disc, especially in the nucleus pulposa, leading to partial herniation and to deformity of the adjoining vertebrae Sometimes there is total destruction of the disc, or more or less severe pinching One of the characteristics of this condition which helps radiographically to distinguish it from tuberculous spondylitis is the frequency of simultaneous destruction and proliferation of bone [FIG. 18]. The prognosis is good and uneventful recovery may be expected, in most cases, without surgical intervention, but in severe cases some permanent loss of movement may result from ankylosis of joints The illness complicated by spondylitis may be neither long nor severe, as in the following case in my series.

CASE 1103. The patient was a man aged 70, who was first diagnosed [illegible] of the joint between the ninth and tenth dorsal [illegible] jacket, and a skiagram taken two months after the first one showed a complete disappearance of the involved joint and fusion of the two vertebral bodies

X-ray confirmation is not always available and indeed there must be many mild cases in which no bony changes detectable by X-rays occur, as it has been shown that in the early, *painful* stage of *Brucella* spondylitis, beyond which stage presumably some cases never progress, no radiological signs are present [190]. I find it, indeed, difficult to believe that the severe pain in the back and neck which is such a common feature of this disease, and which is distinct from the usually fleeting toxic myalgia common to all fevers, is not sometimes due to involvement of the spine. *If this is so, then the favourable* prognosis does not justify *the withholding of appropriate* treatment to relieve pain, hasten healing and limit deformity and disablement, not to mention saving the patient from unnecessary surgery (as in Spink's CASE 220). *It is worth noting that Brucella* spondylitis in the lumbar region may give rise to a *psoas abscess* [30, 347]. Though the spine is the most usual site for suppurative *Brucella* lesions, *it is not* by any means the only one. *Brucella*

abscesses in the soft parts have been reported by Grilichess [150], Buser-Pluss [45], Weed *et al.* [366], and the last workers also encountered suppuration of the hip, knee and shoulder joints. Gardner *et al* [135] had a case of *Br. melitensis* suppuration round the eighth left costo-sternal junction *Osteomyelitis* of bones other [illegible]

[illegible] aged 2, after falling out of bed, from which *Br. abortus* was grown in pure culture; and an abscess of undiscovered origin behind the angle of the jaw. The causative organism has also been isolated from the joint fluid, paravertebral abscess, etc , in many cases [169, 190], and although *Br suis* attacks bone more readily than the other two species, both *Br abortus* and *Br. melitensis* are often involved

CASE 737 Another patient of mine, a woman aged 52, had a severe illness with a fever lasting about 9 months This patient's illness started in the middle of July with fatigue, occasional sweats and pain in the neck Then in October she became febrile and her throat was very sore, getting better for a few days and then relapsing Cough now became troublesome, [illegible]

pain and immobility in the neck and upper dorsal region This pain spread gradually and became localised in the neck and mid-dorsal region, accompanied by girdle pains and a 'very sore back'. The spleen at this time became enlarged The back was very tender in the region of the seventh dorsal vertebra, but there was no redness or swelling in the back and no changes in the leg reflexes Her temperature chart throughout was typically undulant She was given relief by a plaster bed and early in April the temperature settled and the patient made an uninterrupted recovery Skiagrams taken in mid-March showed 'a lesion present [illegible]

vertebrae is shown ' It was concluded that weakening and rarefaction of the vertebrae had occurred as the result of *Brucella* infection, but another

very competent radiologist (who, however, had never heard of *Brucella* spondylitis) thought the changes seen were old ones associated with an adolescent kyphosis and could not have caused her pain. I leave the reader to judge.

Tenderness over the spine was elicited in only two of my cases, but I agree with Spink that heavy percussion over the spine should form part of the routine examination in suspected cases of undulant fever.[1]

Neck rigidity may, of course, be of neural origin *[p. 91]*, or due to myositis. Pain in, and tenderness of, the muscles of the neck and other parts of the body are uncommon. Sometimes there are cramps or temporary weakness of muscles, but I have never seen the more severe though temporary weaknesses, even simulating the foot-drop of alcoholic neuritis, described by Hughes [181].

BLOOD

Passing reference has already been made, when considering the body's defensive reactions *[p. 51]*, to changes of the white blood corpuscles in this disease, but a word must be said first about the erythrocytes.

Anaemia is not a common feature of the uncomplicated disease, but all the same the information about this in the literature is surprisingly scanty. Hughes [181] merely says that 'the red corpuscles diminish rapidly at first, from 5,000,000 to 3,000,000 per cubic millimetre (Bruce), more slowly but steadily later on throughout the pyrexial period leading to the pronounced anaemia which so prolongs convalescence'. Sordelli and Molinelli [258, 328] found a hypochromic anaemia, becoming marked during the course of the disease, in their Argentine cases. These authors were, of course, dealing with cases of *Br. melitensis* infection. Carpenter and Boak [49] have described a secondary anaemia, with a haemoglobin percentage of 60 to 50, and Angle [3] found a secondary anaemia in 87 per cent. of his 100 cases. Spink [333] found very little anaemia, even in his chronically ill cases. My experience is set out in TABLE 7.

It will be seen that *anaemia* was present in only sixty-one of 314 cases (19.4 per cent.), for which the necessary information was available, and in about a third of these cases it was hypochromic.

As regards the leucocytes, the most frequently recorded feature is a *lymphocytosis* associated with a polymorphonuclear leucopenia,

[1] For a good review of *Brucella* spondylitis the reader should consult de Villafañe Lastra and Griggs [99].

supposed to be due to circulating *Brucella* endotoxins, the lymphocytosis being only relative when the total white count is below normal, but becoming positive when the latter returns to normal or above [63, 261] The evidence from my cases with regard to lymphocytosis and polymorphonuclear leucopenia is set forth in TABLES 8 and 9

TABLE 7

EVIDENCE REGARDING ANAEMIA IN 314 CASES OF UNDULANT FEVER

61 CASES WITH ANAEMIA (less than 4 2 million red cells per c mm)			253 CASES WITHOUT ANAEMIA (more than 4 2 million red cells per c mm)		
Normochromic (C I 0 9-1 1)	Hypochromic (C I less than 0 9)	Hyperchromic (C I more than 1 1)	Normochromic (C I 0 9-1 1)	Hypochromic (C I less than 0 9)	Hyperchromic (C I more than 1 1)
34	21	6	159	87	7

TABLE 8

EVIDENCE OF LYMPHOCYTOSIS IN 539 CASES OF UNDULANT FEVER

TOTAL NO OF CASES WITH LYMPHOCYTOSIS (more than 30 per cent lymphocytes per c mm) 452		
NO OF CASES WITH *absolute* LYMPHOCYTOSIS (more than 3 000 lymphocytes per c mm) 230 (50 9 per cent)		NO OF CASES WITH ONLY *relative*
More than 3,000 but less than 5,000 lymphocytes per c mm	More than 5,000 lymphocytes per c mm	LYMPHOCYTOSIS
177	53	222

It will be seen that of these 539 cases, 452 (83 9 per cent) had a lymphocytosis, but it was absolute in only 42 7 per cent As regards polymorphonuclear leucopenia, this was present in 49 2 per cent of 724 cases and was absolute in 39 0 per cent

The complete temporary disappearance of eosinophil leucocytes at some stage in the course of this disease has been noted by various

workers [258, 261, 327], and in 408 out of 570 of my cases (71 6 per cent.) this was the case. In 36 cases, however, there was an *eosinophilia* (more than 3 per cent. of eosinophils) which was absolute (more than 300 per c.mm.) in twenty-two cases.

TABLE 9

EVIDENCE OF POLYMORPHONUCLEAR LEUCOPENIA IN 724 CASES OF UNDULANT FEVER

TOTAL NO OF CASES WITH POLYMORPHONUCLEAR LEUCOPENIA (less than 50 per cent. of polymorphonuclear leucocytes per c mm.)		
356		
NO. OF CASES WITH *absolute* POLYMORPHONUCLEAR LEUCOPENIA (less than 3,000 polymorphonuclear leucocytes per c mm.)		
275		
Less than 3,000 but more 2,000 polymorphonuclear leucocytes per c.mm	Less than 2,000 polymorphonuclear leucocytes per c mm.	NO. OF CASES WITH ONLY *relative* POLYMORPHONUCLEAR LEUCOPENIA
125	150	81

Recently Royer, Molinelli, and Noir [312] have examined by paper chromatography the blood proteins in cases of this disease and found that though the total proteins remain constant, there is a relative reduction of albumins and increase of globulins, especially α and γ. Then as the disease fades the albumins increase again but never to normal, whilst the α and β globulins decrease almost to their normal value On the other hand the γ globulins stay high in nearly every case, even in persons who have had no symptoms of the disease for a long time.

Finally there is an undoubted tendency in some cases of this disease to *bleeding*, presumably due to the action of *Brucella* endotoxin, but it is curious that this phenomenon was so uncommon in Hughes' cases, e g. only five cases of epistaxis In my series there was bleeding from the nose (126 cases), intestine (25), lungs (17), stomach (4), womb (4), and tongue, lips, mouth and cheeks (1 each) The following case is of interest in this connection:

CASE 362 The patient, a girl aged 5, was taken ill suddenly on 9 December with fever and restlessness but no other symptoms On 30 December she was admitted to hospital with a shower of fine râles over the middle of both lungs These soon disappeared. On 31 December she had a blood-stained nasal discharge. Her blood count that day showed

5.89 million red cells, 82 per cent haemoglobin (C.I. 0.7) and 5,600 leucocytes of which 55 per cent. were lymphocytes. On 6 January there was a sudden onset of bleeding from the mouth, cheek and lips, also several haemorrhagic spots on the trunk and limbs. These haemorrhages continued and by 7 January her red cell count had fallen to 4.64 million (C.I. 0.83) with 92,000 platelets. On 9 January there was haematuria, but the bleeding gradually moderated, though on 20 January there were still many blood crusts on the lips and fading purpuric spots on the arms and legs. On 11 January a blood count had shown 2.18 million red cells (C.I. 0.93), and 32,000 platelets and she was given a transfusion of 200 c.c. of blood. On 13 January she had 2.4 million red cells and was given another transfusion of the same amount. Up to this time the temperature had been rising at about 6 p.m. each day to a maximum of 105°F (40.5°C.), with a sudden fall of up to 5°F at night and a suggestion of undulation in the chart, but, curiously enough, no sweating. On 18 January, in spite of the transfusions, her red cells had sunk to 1.83 million (C.I. 0.9) with 18,000 platelets, so she was given a third transfusion, this time of 300 c.c. From this time she began to improve, but on 2 January she was given a subcutaneous injection of 0.2 c.c. snake venom (Water Mocassin, *Agkistrodon piscivorus*) and further injections of 0.3 c.c. on 25 January and 0.4 c.c. on [illegible]

[illegible]

uninterrupted

RETICULO-ENDOTHELIAL SYSTEM

A description has already been given [p. 50] of the important changes due to *Brucella* in the reticulo-endothelial system. Enlargement of the *lymph glands* varies very greatly in frequency in recorded series of cases. Hughes says that 'localised but slight swelling of the lymphatic glands may appear ... those in the neck and groin are most often affected'. [illegible]

[illegible]

two well proved cases of *Brucella* lymphadenopathy in Malta and reviewed literature on this subject, noting the conflicting statements therein. As Bloomfield [26] has pointed out, it is important to distinguish specifically *Brucella* enlargement from that due to other causes, but from the diagnostic angle it is of some importance to bear in mind the occasional enlargement of the mediastinal and

mesenteric glands, and the possible confusion between undulant fever and Hodgkin's disease [p. 120]. Loffler *et al.* [225] found enlarged lymph glands in 10 per cent. of their Swiss cases In my series the lymph glands were enlarged in sixty-eight cases (4 5 per cent)

Enlargement of the spleen is far more common Marston wrote that 'the splenic volume is invariably increased; but not greatly so'. *Hughes [181] says that 'the spleen can nearly always be made out on* percussion and palpation below the margin of the ribs and occasionally is considerably enlarged, especially in malignant cases'. Spink [333] detected splenomegaly in almost half of the patients from whom *Br. abortus* was isolated and in only one-fifth of those culturally negative. In his opinion the activity of the disease could be correlated with the presence of a palpable spleen. Castañeda's [55] experience is very similar. In my series enlargement of the spleen was detected in 332 cases (22·1 per cent.), the spleen being in addition tender in about a quarter of these cases. The splenic enlargement was usually very moderate, the spleen being only just palpable in most cases, but in ten cases it was three fingers' breadth or more below the costal margin, and in one of these cases it extended as far down as the umbilicus In several cases I noted that the fluctuations in the size of the spleen corresponded to the rise and fall of the daily maximum temperature.

Enlargement of the liver is not so common Hughes says that 'the liver is often tender to pressure and slightly enlarged downwards in severe cases, at an early stage and also towards the end of prolonged attacks, when from continued back pressure congestion, it has become somewhat "nutmeg" in character'. Spink [333] has produced evidence in support of the contention that the great majority of patients with this disease have had inflammatory lesions in their liver parenchyma, such as have been already described [p 50] and one of his patients, with *Br. suis* infection, had calcified areas in the liver and spleen, as shown radiographically [333a] These inflammatory changes progressed far enough to produce jaundice in only two of his cases *Cirrhosis* may also be the consequence *of a severe hepatitis [16, 56, 199, 231, 333]* though the influence of drug treatment must always be taken into account Janbon and his co-workers have described a case with Banti's syndrome [191] in which *Br melitensis* was grown from the removed spleen I had a similar case in 1932, though unfortunately the organism was not recovered from the spleen In this case the

pathologist reported that there was no increase of fibrous tissue in the spleen, though, according to Osler, the whole gland should be in an advanced stage of fibrosis However, the long history, secondary anaemia with a low colour index and a marked leucopenia, the haemorrhages, and finally the ascites were all present. Splenectomy did not, unfortunately, save the patient who died as the result of retention of urine, cystitis and pyelitis Leon and Aguirre [217], in a study of 150 proved cases of undulant fever due to *Br. melitensis*, found that 101 (67·3 per cent) had *diabetes* and 114 *liver deficiency* (of these seventy had both) Diabetes terminated the first case in my series [p 113]

[illegible]

found than her *Brucella* infection, the onset of which dated back to five years before cirrhosis was diagnosed This patient died eighteen hours after an operation for omentopexy *Jaundice* was present in eight of my cases The changes produced in the bone marrow have already been mentioned [p 50] and the presence of *Brucella* in this tissue is of importance for diagnosis, but it gives rise to no local symptoms

RESPIRATORY TRACT

Nasopharyngeal catarrh is not common but was present in thirteen of my cases *Bronchitis* usually occurs in severe cases but transient râles are not very uncommon in milder cases Hughes [181] says 'about the beginning of the third week, or earlier in severe cases, some bronchial cooing becomes audible on auscultation, being most marked posteriorally at the base of the lungs Later on, in some 95 per cent there is evidence of basal congestion, varying in amount according to the severity of the general condition ' Such frequency of bronchial signs cannot have been due entirely to the fact that the species concerned was *Br melitensis*, as Castañeda [55], dealing with the same species in Mexico, had only one case of bronchitis (chronic) and one of bronchopneumonia among 245 cases of undulant fever Spink [333] does not even mention bronchitis In my series there have been thirty-four cases of *bronchitis* and ten of bronchopneumonia Hughes remarks that 'in malignant cases this [the bronchitis] is apt to go on to lobular consolidation and hypostatic pneumonia' His whole description is, in fact, that of bronchopneumonia rather than lobar pneumonia Nevertheless *lobar pneumonia* does

occasionally occur. Castañeda observed one case, and Spink described one case, or possibly two. In my series there were five cases, one confirmed by X-rays, apart from one of hypostatic pneumonia

As regards *pleurisy* Hughes [181] says that a dry pleurisy is not uncommon, leading to permanent adhesions, whilst pleurisy with effusion may accompany pneumonic trouble, but is not commonly marked. *Spink [333]* reports two cases, one with effusion, and Maldonado-Allende [244] reviews the literature and reports four cases of his own. Hardy, Jordan, and Borts [158] isolated the organism from the pleural fluid in one case. In my series there were nine cases, four of them with effusion and one with an *empyema* as well, of which Hughes never had a case, but one has been reported by Macdonald [236] My case of empyema was fatal, as was also one of pleurisy, in which the pleurisy was followed by a bilateral bronchopneumonia.

ALIMENTARY TRACT

As has been already mentioned [p 48] the first localisation of the invading *Brucellae* in the tissues is, in most cases, the lymph glands, and there is some evidence that the organisms entering the mouth tend to localise in the *tonsils.* One of my cases developed a peritonsillar abscess, but this was after seven years of undulant fever and *Brucella* was not grown from the pus. The other affections of *the nasopharynx in this disease occur, presumably*, after the organism has invaded the bloodstream. Hughes says that 'the pillars of the fauces, the uvula and tonsils are usually red, relaxed, slightly congested, and dry at the onset of the disease, while the patient [illegible] film or greyish

and remains so in proportion to the condition of the tongue and stomach and to the suitability of the food. There is often some swelling or tenderness, with hardening of the cervical or submaxillary glands These can be distinctly felt and vary in size from a pea to a hazel nut ' Inflammation and enlargement of the tonsils were noticed in eight of my cases and in two cases the fauces were ulcerated *Pharyngitis was present in 265 cases* (17·7 per cent.), and in two of these there was actual bleeding from the throat *Stomatitis* was present in thirty cases, with ulceration in twenty-two of these, a condition regarded by Poston and Menefee as rare [291]. Some of *my patients complained of a nasty taste in the mouth or a nasty*

smell, and I have noticed that this is sometimes so characteristic that when the patients have relapsed, or possibly been reinfected, after a considerable interval of freedom from symptoms, the return of this taste or smell has made them assert categorically that they were now suffering from the same disease as before. Castañeda has called attention to the part played by dental sepsis, especially root abscesses, in increasing the severity of the disease, and he says that all his cases with osteo-arthritis had co-existing abscesses or pyorrhoea Actual *glossitis* was noted in only five of my cases, there being ulceration in two, but furring of the tongue is the rule and disappearance of this fur is, in my experience, one of the very few reliable indications that the patient has re-adjusted, for the time being at least, his relationship with his parasite—or, in other words, that 'recovery' is at hand. As Hughes remarks 'it may, therefore, be taken as a rough but useful rule that a fall of temperature to normal will rarely prove permanent unless at the same time the tongue has also become clean'

The *stomach* is also very often affected in this disease and Hughes has no hesitation in attributing to gastritis, not merely the furred tongue and foul taste in the mouth but also loss of appetite, indigestion, epigastric tenderness and sometimes pain, nausea and vomiting. About half of Maclean's [228] New Zealand cases had [illegible]

digestion, flatulence, tympanites, abdominal discomfort or distention in twenty-seven cases, abdominal tenderness in 181 cases (12·1 per cent), abdominal pain in 114 cases (7 6 per cent), nausea in forty-one cases and vomiting in eighty-three cases These phenomena were not, of course, always entirely attributable to irritation or inflammation of the stomach, as the *intestines* were certainly involved sometimes and even the *gall bladder* Although *constipation* is the rule and was present in 589 of my cases (39 3 per cent), *enteritis* is probably not uncommon in this disease and I find that though I have recorded 'acute enteritis' in only one case, *diarrhoea* was present in eighty-one cases, and two other patients had offensive stools Bleeding from the intestine has already been mentioned [p. 78]. As regards the *gall bladder* I can find no mention of it in Hughes and yet it is a well established fact that this organ is a favourite hiding place of *Brucella* Spink [333] had three cases of

cholecystitis, in one of which gall stones were present [p. 92]. *Castañeda [55] had three cases of gall bladder pain and knew of three* other cases, in none of which was *Brucella* grown from the bile after cholecystectomy, but nevertheless the symptoms disappeared in all cases. *Brucella* has been grown from the bile by many workers [2, 140, 158, 258] *who have described the thickening of the walls of the* gall bladder with lymphocytic and plasma cell infiltration of the stroma, and sometimes typical granulomata [p. 49]. In my series *there was tenderness over the gall bladder in forty cases.*

A fatal case of pancreatitis in Scotland was described by Beattie, Smith, and Tulloch [16] and Leys [221] had a case suggestive of the same diagnosis.

CARDIOVASCULAR SYSTEM

The pulse in most cases is slow in proportion to the temperature, at any rate in the early stages [181], but in serious cases, especially when the lungs are involved, *tachycardia* is the rule and the pulse is apt to become thready as the burden on the heart becomes too great. In one of my cases (CASE 1426), which lasted eight weeks, *bradycardia* was present throughout, in spite of a temperature swinging up to 103°F at night and a state of anxiety for much of the time. Tachycardia was, however, noted in eight of my cases, in three of which it was accompanied by mental irritability, confusion, trembling, etc., suggesting a toxic condition. Spink [333] considers that the myocardium *is not adversely affected, at any rate in a* specific manner, and it is true that at all his post-mortems Hughes found the myocardium normal, *except in one case in which it was* 'flabby.' Nevertheless, Uhlhorn [360] and Olin [274] have described cases and Loffler, Moeschlin, and Willa [225] state that *myocarditis* is 'not infrequent' in Swiss cases. In several of my cases there was cardiac distress, dyspnoea, *tachycardia, oedema of the ankles, etc.,* with no evidence of kidney disease or phlebitis, suggesting temporary cardiac incompetence due to toxaemia.

Brucella endocarditis has already been mentioned [p. 49] and cases *have been described by many* authors [143, 159, 164, 221, 300, 308] (in No. 234 of the Bibliography will be found a review of the literature on this affection), and the fact that all my five cases and all Spink's three were fatal indicates the seriousness of this complication, even in these days of antibiotics. It would seem probable, too, that short of infection *Brucella* toxins may hasten the course of coronary disease, as Spink has suggested in one of his cases.

Manchester [245] is inclined to go further and consider long continued undulant fever as a primary cause of coronary disease, whilst Peery [284a] has produced evidence suggesting that *Brucella* endocarditis is one of the chief causes of calcifying aortic stenosis

Phlebitis, often with thrombosis, is a complication which Spink complains has been much neglected in the literature He describes three of his cases in which this occurred, one with thrombophlebitis of a peripheral leg vein being nearly fatal, and he quotes a published case in which death occurred. A case in Tunisia was described by Debbasch [92] in 1931 in a woman of 25 who, after two months of continuous undulant fever, had sudden pain in Scarpa's triangle, swelling of the left leg, oedema and cyanosis The condition steadily cleared and was not affected by a recurrence of fever Olin [274] had thrombophlebitis in four of his cases and Loffler *et al* [225] say that this complication has been common among their Zurich cases Foshay [126] says that 'thrombophlebitis occurs and deaths from embolism are not rare' Foggitt [123] has described an interesting case in a fish-dock worker aged 30, who after suffering from undulant fever for two years developed a painful phlebitis in both legs This condition disappeared but his disease continued and at the end of the third year of the disease he developed a subacute anterior uveitis of the right eye, and two months later an acute periphlebitis of the superior temporal retinal vein of the left eye In my series there has been one case of phlebitis, in the left leg, without thrombus formation I also had one case of cerebral thrombosis, with aphasia and agraphia, for which no other origin than the *Brucella* infection could be found

Two of my cases had *clubbing of the fingers*, in one (CASE 1238) there was a subacute bacterial endocarditis due to *Brucella* superimposed on an old rheumatic, aortic stenosis [TABLE 16, p 154], but in the other no abnormality of the heart could be discovered

GENITO-URINARY SYSTEM

The *urine*, according to Hughes, 'is decreased in amount at first and in severe cases dark in colour and loaded with lithates Later on, unless there is much diaphoresis, it may be increased in amount, light in colour and of low specific gravity It is acid in reaction, except in a few instances when temporary irritability of the bladder is present Albumen is rarely present, even in fatal cases retention may occur in severe cases' *Albuminuria* was present in eleven of my cases In two of these, both fatal, there was serious renal damage revealed at autopsy, but not in the other nine, though in all

but one the albuminuria was slight and transient, being very pronounced, *for no discoverable reason, in the remaining case.* Apart from the two cases just mentioned, one of which (CASE 212) had multiple septic cysts in the right kidney and died of uraemia, and the other (CASE 323) emboli in both kidneys, there was only one case of *nephritis in my series and three cases of pyelitis* It is a striking fact, as Bickel [22] has pointed out, that though, as the Mediterranean Fever Commission first showed, *Brucella* can frequently be grown from the urine of cases (from about one-third of his cases), *yet serious inflammatory conditions of the urinary tract* with *Brucella* are rare. This author describes two well investigated cases of *pyelonephritis*, and others have been described by Spink and other authors Cases of *pyuria* were reported by Leys [221], and Forbes *et al.* [124], and several cases of *cystitis* by Hardy, Jordan, and Borts [158] I had one case of cystitis, one of pyuria, two of dysuria, two of incontinence of urine, eleven with frequency of micturition, of which one had difficulty as well, and another scalding, and two with retention of urine.

As regards the sexual organs it is well known that *Brucella* often attacks the *testicles* and *epididymis.* Hughes said this occurred in about 4 to 5 per cent. of his cases and was usually unilateral and he notes that these lesions often occur during relapses, which has also been my experience. Suppuration is uncommon, but occurred in one of Hughes' cases. In acute *orchitis* the testicle and epididymis often swell rapidly, greatly and painfully. There may be some redness of the scrotum and effusion into the tunica vaginalis Though the acute inflammation only lasts a few days, the hardness usually takes much longer to disappear In Spink's cases the incidence of orchitis was just over 2 per cent , but Castro [66] (who reviews the whole subject in great detail) had an incidence of 14 per cent of his cases in Uruguay, and it seems to be common too in the Argentine [263] Morana [267] reported in 1950 that he had seen very few instances of orchitis in Malta among the hundreds he had treated in the preceding ten years Janbon and Bertrand [189], reviewing its occurrence in chronic cases, state their conviction that sterility from this cause is well authenticated, in which they are supported by Balze *et al* [7], who describe seven cases of epididymo-orchitis and six of epididymitis Mathur [248] has reported seven cases *from the Punjab Three cases of suppurating* epididymo-orchitis have been described by Puig [294] and two more by Tapie *et al*

[350], and a very severe necrotic case by Gadrat *et al* [133] In my own series there were only nineteen cases of orchitis, with definite atrophy in one case, and one case of epididymitis Bevan [21] has reported a case of *vesiculitis* of nine months' duration in Rhodesia.

Turning now to the effects of *Brucella* infection on the female genitalia, all portions may be involved *Mastitis* is said to be not infrequent in undulant fever [158]. Amoss and Poston [2] isolated *Brucella* from the right *ovary* and tube of a patient convalescing from undulant fever and Harris [160] had a similar experience. *Brucella* infection undoubtedly interferes with menstruation, producing *dysmenorrhoea* (Nagel [269], and one of my cases), *menorrhagia* and *metrorrhagia* [p. 78]. These disturbances are due to circulating *Brucella* toxins, but actual infection of the womb also

guinea-pig inoculation of an extract of the entire foetus and placenta [50] Simpson and Frazier [325] reported five cases of repeated abortions in women with positive agglutinin tests but negative Wassermann reaction All drank raw milk. Similar cases have been reported by de Carle [95], Frei [130], Gray [144], Janbon and de Kerleau [192] and Chassagne and Gaignoux [68] Del Vecchio [97] examined 391 women in the rural areas of the province of Bari, Italy, where foci of animal infection had been demonstrated One hundred and fifty-nine women had inapparent *Brucella* infection and 78 6 per cent of these aborted The organism was isolated from two of these cases and the others had positive agglutination

In my series there were three cases of abortion and two of miscarriage (one of these women had two miscarriages), not proved culturally but with agglutination titres of 1 in 2,500, 1,250, 1,000, 250, and 100 respectively One of my patients was delivered of a healthy baby at full term, though she had then been suffering from undulant fever for ten months Spink [333] is inclined to believe that *Brucella* is not more apt to produce abortion in a woman than other pathogenic organisms, and certainly the contrast between its potency in this respect in some animals and man is striking

EYES

Eye affections, ranging from sore eyes or slight lack of visual acuity to complete blindness occur in this disease, but their causation has been much disputed Obviously the eye can be infected directly

from the outside, or following an infection of the blood, or finally the ocular manifestations may be the result of an allergic reaction in a sensitized person. It is extremely unlikely that only one of these three mechanisms is concerned in all cases. Affections of every structure of the eye, as well as the external ocular muscles, have been described, including conjunctivitis of various kinds, episcleritis, keratitis with or without ulceration, haemorrhage into the anterior chamber, uveitis, iritis, iridocyclitis, choroiditis, cataract, haemorrhage into the vitreous, retinal oedema, haemorrhage, and periphlebitis; papilloedema, optic neuritis and optic atrophy; paralysis of the internal and external eye muscles, partial or complete; and finally glaucoma. Useful reviews of the literature have been given by Green [145], Cremona [79], Pagliarani [280], and most recently by Foggitt [123]. It would seem that *Br. melitensis* is more liable than *Br. abortus* to give rise to these troubles, as though in most countries ocular disturbances due to *Brucella* are seldom reported, Molinelli *et al* [261] found them in forty-one out of ninety-five patients examined and in about half these cases the fundus was affected; and in the series described by Cremona [79] (also in Argentina) eye lesions were found in 55 per cent. of the eighty-nine cases examined, the commonest being venous congestion of the fundus (47 per cent.) and allergic conjunctivitis (21 per cent.). In my own experience many patients complain of tiredness in their eyes or some difficulty in reading [86], which seems to be due to a temporary weakness of accommodation. In my CASE 1 [p. 113] (which probably lasted forty-seven years) the patient complained that she had been forced after a time to give up the fine needlework of which she was fond as she found it too great a strain on her eyes. In my other cases apart from tiredness, aching, burning, soreness, etc., there were definite lesions in only ten, viz. five cases of conjunctivitis (one phlyctenular), and one case each of choroiditis, scotoma, retinal thrombosis, retinal periphlebitis and uveitis.

It is impossible at present to be sure in many cases whether these eye troubles are due to actual *Brucella* infection of the eye, to circulating *Brucella* endotoxins, or to a true allergic reaction in a sensitized subject.

NERVOUS SYSTEM

Any long continued fever is apt to affect the patient's morale, and this must be especially true of one which fluctuates up and down day after day and week after week for months, or is continually

encouraging false hopes of cure by intermissions of several days or

brightened the picture, relapses after antibiotic treatment are not at all uncommon and must be additionally disappointing for the patient who has hoped so much from a 'wonder drug'. And lastly there is a hard core of cases which either does not benefit from antibiotic treatment or cannot tolerate these drugs

One of the striking features of this disease, is the marked fatigue, weakness and debility it engenders at the time (76·1 per cent of

Hughes [181] remarks that 'nearly all patients become low spirited when their temperature returns to normal at all quickly after remaining high for any time' The neurosis due to the illness itself is sometimes gravely aggravated by the failure of the physician to find the true cause, or indeed his refusal to admit that the patient's condition has any physical basis [p 109] At the same time the *Brucella* toxins have an irritative effect on the nervous system

More serious nervous involvement sometimes occurred, especially in

in otherwise mild cases, are usually transient and ascribable to *Brucella* toxaemia, but more serious changes may be involved, such

as cerebral thrombosis [p. 85], rupture of a mycotic aneurism [157], true meningitis or meningo-encephalitis [23, 158, 189, 212, 225, 263, 274, 292, 321, 357], of which I have had three cases *Brucella* has been grown from the brain or the cerebrospinal fluid in a number of cases [181, 315, 333] Meningismus, too, has been described [36, 159, 221], and I have had three such cases

A case described by Hobbs [170] gives a good picture of the toxic type of case without meningeal involvement.

The patient, a woman of 56, felt 'out of sorts' on 14 November and on taking her temperature found it was 102°F. (38·9° C.) She felt chilly, had headache and pain in the right side of her chest. Apart from a rapid pulse there were no abnormal physical signs. The temperature fell gradually, but rose again on 26 November and the evening maximum continued to rise till on 6 December it was 101°F. (38 3° C.). At this stage she was looking ill, had a cyanotic tinge to her lips and face, her tongue was very furred, her pulse rapid, her abdomen tender all over and she was rather constipated She also had pains in other parts of the body, especially the head and less often the back, chest and legs There was a slight cough and a few râles were heard at the right base. The temperature now fell again until 12 December, but on 17 December it rose again The abdomen was now rather doughy and tender, especially in the right iliac fossa There was much flatulence and the patient was very constipated The spleen was not palpable. The pulse was persistently over 100 and the 'rheumatic' pains continued, especially in the calves, head and neck. *She had drenching night sweats. Towards the end of* December she developed several scaly red patches on the arms and buttocks, not unlike the rose spots of typhoid She now steadily improved and by the first week of February she was well enough to go to Eastbourne to convalesce. Though whilst there her evening temperature was 100° *to* 101°F (37 8° – 38·3° C) she did not stay in bed and when first seen by Dr Hobbs on 28 February her temperature was 101 4 F. (38 6 C) Her tongue was clean but she still had slight abdominal tender-

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typically undulating fever was now more marked than before, the waves taking five to seven days to rise to a peak and the same to descend At the peak there were rigors and the abdominal tenderness and discomfort were *increased, especially over the region of the gall bladder* There was much mucus in the stools The patient now had delusions of persecution and often refused food on the grounds that it was poisoned (my case 325 had

exactly similar delusions) The sweating was still very heavy and the patient felt faint on the slightest exertion During the illness she lost about 2 stone in weight The blood serum taken on 11 April agglutinated *Br melitensis* to 1 in 125 and *Br. abortus* to 1 in 250 The blood count showed a leucopenia with an absolute lymphocytosis

The following case, on the other hand, showed definite meningismus·

CASE 99. The patient was a girl of 17 who had been out of sorts, headachy and very irritable (which was very unlike her) for two to three weeks before the sudden onset of fever on 20 May with a rigor and repeated vomiting This vomiting recurred on the two following days She had a bad headache, felt very tired and was constipated On 24 May her temperature was 102°F , the tongue thickly coated with yellow fur, she had severe frontal and occipital headache and pains in both ankles and knees On examination nothing abnormal was discovered A lumbar puncture was done, but the cerebrospinal fluid was normal On 25 May her temperature was 102°F , the headache was purely occipital and she had some neck rigidity with pain on flexing the head Next day there was tenderness in the epigastric, splenic and right iliac regions, and she developed acute deafness in both ears, without pain, and the drums appeared normal The bowels were now open, the stools being pale brown, loose and offensive The headache, neck rigidity, vomiting, pains in the joints and deafness were all transient There was a trace of albumin in the urine, but this disappeared in a few days On 30 May her blood serum agglutinated *Br. abortus* to 1 in 250 and the titre was the same on 6 June Within a week the bowels became normal and by 7 June the patient felt much better Her appetite returned, but her night sweats were still heavy. The abdominal tenderness persisted and the liver and spleen were found to be enlarged On 24 June she got up and by the end of the month she went out, but her temperature still had a tendency to rise for a little while longer

Transient aphasia and deafness, with tinnitus and paraesthesia has also been reported by Dixon and Roaf [100] Spink [333] has suggested that this tendency of *Brucella* to attack the eighth cranial nerve explains the frequency with which tinnitus and deafness were encountered when streptomycin was first used in the treatment of this disease [p 137] Roger [310], who in 1929 gave a comprehensive review of all the nervous complications of the disease due to *Br melitensis* infection, classes spondylitis and sciatica as common, myelitis and polyneuritis as uncommon, and cranial osteitis, cerebral complications (excluding delirium), and true meningitis (not

meningismus) as rare complications. Acute myelitis is mentioned, besides Roger, by de Jong [96] as an occasional occurrence and Debbasch [93] has given a description of a case with sudden onset after six weeks of undulant fever, in which there was a partial paraplegia, epileptiform tremors, bilateral Babinski sign, ataxia, cutaneous and tendon reflexes exaggerated, but no degenerative phenomena

Though, as I have remarked the psychiatric symptoms are usually transient, it is obvious that if the disease becomes chronic the liberation of *Brucella* endotoxin will continue and serious psychiatric manifestations *may occur, as in Spink's* CASE *122 in* which the patient became an alcoholic, then a narcotic addict and attempted to murder a member of his family and then to commit suicide. In this case a pericholecystic abscess containing a pure culture of *Br suis* was opened ten years later and the patient became a normal citizen. I entirely agree with Spink that the mechanism of the neuropsychiatric disorders is obscure and merits investigation.

The misery and mistreatment suffered by many patients with the chronic form of this disease and labelled neurotic is referred to later under chronic brucellosis [p. 109], a subject the implications of which will not be clear until the diagnosis of the disease has first been considered, but there can be no doubt that even in cases correctly diagnosed a neurosis can be present, either due to the long duration of many cases, with the fever and other symptoms fluc*tuating up and down day after day and week after week for months,* or constantly encouraging false hopes of cure by intermissions of several days followed by the familiar and hated burning afternoons and drenching nights, or by the direct influence of the *Brucella toxins upon the nervous system Janbon and Bertrand [189] suggest* that though the origin of *Brucella* neurosis (*patraquerie brucellienne*) is obscure, the chief trouble is in the autonomic system, which is irritated as a result of sensitisation of its nervous tissue to *Brucella* antigens *This effect, they maintain, implies the survival of Brucella,* deeply hidden

The suggested relationship of brucellosis to disseminated (multiple) sclerosis is considered in the differential diagnosis of *undulant fever [p. 120]*

BRUCELLA SENSITIVITY

Hypersensitivity to *Brucella* antigen has already been discussed in connection with the occupational arm rash of veterinary surgeons [p 42], but a rather fuller consideration *will be appropriate at this*

stage Veterinarians are not by any means the only people who [illegible]

later in connection with diagnosis [p 106] and here I would only remark that a high proportion of persons who have had *Brucella* infection give a positive intradermal test, even when they have apparently completely recovered from their infection, but whether this is an indication of the continued presence of *Brucella* in the body is not known Foshay [126] has reported a case in which a *Brucella* infection, which had been quiescent for six years, was lighted up by an intradermal test, with the result that the patient was disabled for almost a year afterwards

As I have already remarked with regard to disturbances of the nervous system, some symptoms commonly encountered in this disease, such as certain skin rashes, some eye conditions, nausea, indigestion, headache, sore throat, meningismus, appear to be often allergic in nature, as may be judged by the sudden appearance of these signs and symptoms when an intradermal injection of a *Brucella* antigen is given to a hypersensitive patient The extreme degree of specific sensitivity possessed by some patients is illustrated by one of Griggs' cases in which he could not find a dilution of antigen sufficiently great to avoid a local reaction when injected intradermally. In one of my cases (CASE 1315) the intradermal injection of 0 1 ml of a 1 in 1,000 dilution of Brucellin (the skin test dose being 0 1 ml of the full strength) produced an area of erythema and induration 3·5 cm by 5 5 cm, and in another case (CASE 619) injection of the normal skin dose caused a very marked local and general reaction with the ultimate formation of a slough

CHILDREN

Before leaving the clinical features of this disease a word must be said about its characters in children There seems every reason to [illegible]

case in which a premature child (6½ months) very soon after birth exhibited sweating, enlargement of the cervical glands, feverish attacks, anorexia, flatulence, constipation and later catarrh, foul stools, loss of weight, otitis media, bronchopneumonia, leg abscesses,

pharyngitis, etc. This illness continued with fluctuations for two and a half years. The blood culture was negative, but there was agglutination to 1 in 100, the complement fixation test was positive, and there was anaemia and a persistent, marked, absolute, lymphocytosis.

The varying liability to infection at different ages has already been discussed [pp. 57–60] and it remains only to consider in what respects the clinical disease in children differs from that in adults In my series there were 149 patients under 15 years of age and whereas 32·2 per cent. of these patients had enlarged spleens, only 19 per cent of the older patients in the series showed this sign Again 11·4 per cent. of the children had enlarged livers as against 4 9 per cent. of older patients; 18·8 per cent. had adenitis, as against 2·7 per cent.; and 14·8 per cent. had a rash, as against 6 9 per cent of older patients. The most striking difference was, however, the extraordinary mildness of the disease in many of these children One child of 8 had no other manifestation of the disease than fever, though this lasted seven weeks. In another case, lasting six months, only fever and sweating were recorded, whilst two other patients had in addition only splenomegaly in one case and a rash in the other. In four cases apart from fever the only complaint was malaise and in many cases, two of which had fever for eleven months and six months respectively, malaise was consistently denied The disease in fact tends to be mild in children under the age of puberty, though two of my fatal cases were aged 21 months and 8 years respectively. Williamson and Gibson [370] have recorded a case in a child aged 20 months who, though he suffered for several weeks from an undulant fever, rising at times to 102°F., looked quite fit throughout his illness and was not even prostrated at the height of his fever

Here I have been referring to the natural course of the disease, for, excepting duration of fever, no difference of the features to which I have just referred is detectable between my eighty-one cases preceding the introduction of antibiotics and the sixty-eight subsequent cases in children As regards the duration of the disease, the average duration of fever in my children was 12·9 weeks (as against 17·1 weeks in older patients), and whereas the average duration of the pre-antibiotic cases was 11 weeks, that of the post-antibiotic cases was 13 2 weeks

8

DIAGNOSIS

CLINICAL DIAGNOSIS

This is not a disease in which a firm diagnosis can be made on purely clinical grounds, but certain features should suggest the possibility of undulant fever being present and should lead to appropriate procedures to prove or disprove this assumption One can go further and say that not infrequently cases occur in which the circumstances, or the clinical features, are so suggestive of *Brucella* infection that nothing can absolve the physician from the duty of making determined and repeated efforts to prove or disprove this suggestion.

The circumstantial evidence which may suggest the diagnosis is the consumption of milk or milk products proved to be infected with *Brucella* [pp 36–39], or special exposure to infected materials, usually on account of occupation [pp 40–46].

Clinically an undulant temperature chart, heavy night sweats, the presence of high fever with comparatively little constitutional disturbance, and continued fever in the absence of other clinical signs, are all suggestive of the acute disease The chronic form is more difficult to recognise and its features are described at the end of this chapter

DIAGNOSTIC TESTS

Before describing the various diagnostic aids which may be employed to test the provisional diagnosis a word must be said with regard to the general use of such aids and their value The only *conclusive* evidence of *Brucella* infection is, of course, the recovery of the organism from the patient's body or excreta By refusing to make a diagnosis of undulant fever in any case in which the organism cannot, or has not, been recovered it is easy to build up a neat series of cases in which not only is the blood (or other) culture positive in every case, but in which also antibiotic therapy is almost invariably triumphant, as it is the circulating *Brucellae* which are the most easily killed, and usually in such cases the body's non-specific immune mechanism seems to deal easily with the remaining

intracellular organisms. But such a policy seems to me quite unjustifiable, because it distorts the truth and abandons many unfortunate patients, really suffering from this disease, to the consequences of a wrong diagnosis or to the ostracism which so often falls on anyone labelled a neurotic.

On the other hand it is of the greatest importance not to make a firm diagnosis of *Brucella* infection on insufficient grounds and it cannot be too strongly emphasised that all diagnostic tests have not the same value and that the sum of several positive tests, each of small value, is not equal to a single more valuable test when positive. I shall refer to this again when considering chronic brucellosis at the end of this chapter.

CULTURE

By the use of suitable techniques it is often possible to grow *Brucella* from the blood and less often from the spleen, urine, faeces, tonsillar swabs, sputum, bile, lymph glands, sternal marrow, cerebrospinal fluid, peritoneal fluid, pericardial fluid, ovary, Fallopian tubes, pleural effusion, maternal milk, sweat, abscesses (including osteomyelitis and spondylitis), etc, and from the vagina, the placental surface and the vaginal discharge in cases of abortion [126, 156, 158, 169, 255, 258, 263, 327]

Though the extraordinary success reported by some workers in isolating the organism (e g. 'we have yet to see the patient in the first 6 months of illness, in whom we seriously suspected brucellosis, from whom the organism was not recovered' [229]) is probably partly due, as I have indicated above to selection of cases by the employment of different diagnostic criteria, yet all my experience *indicates that in this country attempts to isolate the organism are* made far too seldom and are not persisted in sufficiently.

In my series blood culture was successful in only seventy-one out of the 439 cases in which it was attempted; urine culture was successful in seven out of 201 cases; faeces culture in none of 114 cases; culture from the cerebrospinal fluid in none of three cases; from the spleen in the only instance in which it was attempted; from tonsil swabs in none of five cases, from the bile in one of two cases; from the aortic valves in one case, from the synovial fluid in the only case attempted, and finally *the only eye swab gave a negative result*

Blood culture is obviously more likely to be successful when the blood is taken at the height of the fever, as this usually coincides

with the liberation of large numbers of organisms into the blood stream. But the procedure is worth attempting even in afebrile patients, as Löffler has shown [223] I have occasionally succeeded in obtaining a blood culture which had previously eluded me by administering protein shock by the injection of T.A B vaccine, which apparently drove the organisms into the blood stream, perhaps by producing contraction of the spleen It would appear from the records of work in the Mediterranean countries, Mexico, the Argentine, etc., that the *melitensis* and *suis* species of *Brucella* are easier to grow from the blood than *abortus* [65, 178] The previous administration of antibiotics seems sometimes to interfere with isolation of the organism from the blood and the bone marrow [156], as might be expected

Culture from the bone marrow, either of the sternum or ilium, has proved useful in some hands and is well worth trying when culture from the blood has failed Spink [333] carried out simultaneous blood and marrow cultures in fifty-nine cases and recovered *Brucella* from the marrow in five instances in which the blood cultures remained sterile In no instance were organisms recovered from the blood when the marrow cultures remained sterile Hamilton [156] grew the organism from the marrow of the ilium in twenty-six out of thirty cases.

Description of the technique of culture is outside the scope of the present work, but full descriptions can be found in standard works, such as that by Wilson and Miles [376], and much useful information is contained in the Second and Third reports of the Expert Committee [196, 197] Culture is effected directly on artificial media, or indirectly in the developing chick embryo or the guinea-pig It is only necessary to remark here that the guinea-pig method is specially applicable where contaminated material is concerned, and that the usefulness of culture in the chick embryo is limited by the small size of the inoculum which can be used (more than 0 2 ml is too toxic to the embryo), and is more suited to central or research laboratories Once again it must be emphasised that culture is

glutination test had been consistently negative), but repeated attempts may be necessary before success is attained and with such a slow growing organism sub-culturing must be continued, at

regular intervals from the fourth day onwards, for at least three weeks if necessary.

In cases of obscure meningitis, in which not only serum agglutination, but also blood culture, has been repeatedly negative, culture from the cerebrospinal fluid may be successful [98, 189]

Though *Brucella* usually grows out in five to seven days on a suitable medium, it sometimes grows very slowly[1]; therefore subculture should be continued over a period of at least three weeks In four of my cases the colonies of *Brucella* took twenty, nineteen, eighteen and seventeen days respectively to appear.

SERUM AGGLUTINATION

Since Wright [382] in 1897 first demonstrated the presence of specific agglutinins for *M. melitensis* in the blood of experimentally infected and immunised animals, as well as in the blood of newly infected patients, the agglutination test has been by far the most useful and widely used diagnostic procedure in this disease Nevertheless its value depends entirely on the use of a satisfactory antigen, and it has long been recognised that, if different workers' results are to be comparable and a minimum diagnostic titre established, standardisation of the antigen for the test is essential The first step in this direction was taken when the World Health Organization's Expert Committee on Biological Standardization established an International Standard for Anti-*Brucella abortus* serum in 1953 (of similar agglutinin content to the standard serum of the Office Internationale des Epizooties), thus enabling the establishment of comparable local or national standard sera and so the standardisation of antigens for use in the test The W.H.O. Expert Committee on Standardization has since recommended the adoption of a unit system for standard sera which enables the agglutinating strength

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the International Serum, then titres of 1 in 320, 1 in 160, 1 in 80, 1 in 40 and 1 in 20 obtained with sera under test indicate approximately 640, 320, 160, 80 and 40 Units respectively (It should be noted that these titres refer to the final dilution of serum in the serum-

antigen mixture.) The statement of agglutination content in this way can have but one meaning and ensures a valid comparison with the results obtained in different countries with different methods, which is a great advance However, the expression of agglutination titres in International Units is not favoured by some workers, who think that, as agglutinins are much less clearly defined substances than toxins, etc, the unit system gives rise to a degree of false confidence in the accuracy of the results

Various so-called diagnostic titres have been suggested by different workers using different methods and antigens and it is perhaps of historical interest to note that Bassett-Smith [9] in 1906, examining the blood of 150 patients with various conditions, formed the opinion that 'when using the 1 in 30 dilution (if the technique is properly carried out) a positive agglutination reaction may be considered conclusive of Mediterranean fever, past or present' However, as will be seen from the above remarks, the past arguments as to significant titres have little value unless the antigens then used can be checked against the standard serum

Low titres seem to be commoner when *Br abortus* is involved than when it is *Br. melitensis* which is responsible, and of Castañeda's 1,398 cases with positive blood cultures, 88·2 per cent had agglutinins to a titre of at least 1 in 320 [57]

The great majority of agglutination tests done on the cases in my series, especially since 1938, have been performed by laboratories belonging to or associated with the Public Health Laboratory Service, and although the antigen has been changed from time to time the suspensions prepared in this country have all had much the same degree of agglutinability, especially since 1950, though they have never been tested against the international serum The criteria used for the inclusion of cases in my series have been culture of the

one of them the titre was 1 in 80 and in the other two agglutination was consistently negative) In sixteen other cases with a titre of less than 1 in 100 nine had a titre of only 1 in 80 but in one of these cases, with a duration of over six years and still continuing, there is an extreme sensitivity to *Brucella* antigen, the milk supply of another was from a farm on which there was contagious abortion, another is

a farmer's wife, and all are clinically very suggestive of undulant fever. One case with a titre of 1 in 60 had an infected milk supply and the patient's two brothers contracted the same disease at the same time (titres 1 in 2,000 and 1 in 400). Six cases had a titre of 1 in 50 and were all clinically very suggestive, one of the patients having had an exactly similar illness three years before.

In the great majority of cases, however, the titre was a high one, as will be seen from FIG. 19.

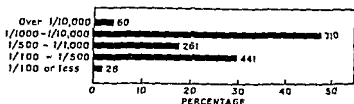


FIG 19 Agglutination titres in 1,500 cases of undulant fever

Even with a standardised antigen the significance of any particular titre is bound up with the difficult question of the persistence of agglutinins in the blood after the disappearance of symptoms It is, of course, a well-known fact that agglutinins against the enteric group of organisms persist often for many years after the cessation of disease and, so far as I know, the great majority of such cases cannot be shown to be carriers of the organism, so that the continued production of agglutinins must be due to the continuing action of a mechanism set in motion, or perhaps brought into being, by the original infection It might, therefore, be argued that the same thing occurs in *Brucella* infection, so that the presence of agglutinins in the blood, at any rate to a low titre, does not necessarily indicate present infection Spink considers that a titre of 1 in 20 to 1 in 80 is 'most likely to be found in patients without other *satisfactory* [my italics] evidence of brucellosis and in healthy persons', quoting other authors and studies at the University of Minnesota in support of this view In the latter studies, for instance, 3·29 per cent. of 255 consecutive patients having negative *Brucella* skin tests had *Brucella* antigens in their blood, and in a second study 18·54 per cent. of 1,627 'presumably healthy blood donors' had *Brucella* agglutinins It will be noticed that the value of these findings as evidence of the presence of *Brucella* agglutinins to a low titre in *healthy* persons (i e free from *Brucella* infection) depends on two assumptions: in the first place that a negative brucellin test is good evidence of the

absence of *Brucella* infection (an assumption which I discuss on p 107), and secondly that the routine examination of blood donors in Minnesota is sufficient to exclude latent *Brucella* infection conclusion which I am not in a position to evaluate Spink conclude from this and other evidence, that 'First, a relatively high incidence of *Brucella* agglutinins can exist in a healthy population or in persons having *unrelated illness; second*, the titres in these people for the most part are below 1 in 100, and third, the titres in bacteriologically proved cases are almost always above 1 to 100' He points out that the high incidence was probably related to the fact that the people came from rural areas where animal brucellosis occurred, which brings us back to the problem I have discussed [pp 42–43] of whether actual infection is necessary to produce sensitisation of the skin or the establishment of the mechanism for the production of agglutinins It also raises the question, which I discuss more fully when considering 'chronic brucellosis' [p. 109], of whether patients with latent *Brucella* infection may show no other signs of their condition than a low agglutinin titre and skin sensitivity

To return to the persistence of agglutinins after an attack of undulant fever, Loffler and Albertini [224] have given evidence for the persistence of agglutinins more than five years after infection and one and a quarter years after splenectomy in a patient who was apparently cured and had no recurrence after a further two and a half years Frei [130] has shown such persistence in a case of laboratory infection in which, though the titre gradually dropped, it was still 1 in 640 four years and five months after an initial titre of 1 in 1,600 Baxter [14] found a very varying rate of fall in titre, in one case from 1 in 500 to negative in twenty-one months, whereas in another it was still 1 in 125 at twenty months after an initial 1 in 1,250. Dooley [101] has given an interesting account of a milk-borne outbreak of *Brucella* infection in a large boys' residential school in Connecticut, U.S.A , in which though 41 3 per cent of 232 boys and young adults thoroughly studied had *Brucella* agglutinins in their blood to a titre of at least 1 in 10 (17 8 per cent had a titre of 1 in 80 or more) [illegible]

December, in another case a titre of 1 in 2,560 in January was still 1 in 120 in December It is interesting to note that in the eleven boys

showing no disease diagnosable as undulant fever and with titres of 1 in 10 to 1 in 40, *the onset of such diseases as pertussis, varicella, 'β-haemolytic streptococcal tonsillitis', etc., sent the titre to Brucella* right up, in one instance from 1 in 80 to 1 in 640 in one week. *Jordan [198] recorded falls in titre in four patients who were* apparently well, in one case an initial titre of 1 in 160 was unchanged after eight months, whilst in another an initial titre of 1 in 320 had *completely disappeared in the same period* Molinelli [258] found that in 80 per cent. of brucellosis cases in Argentina (mostly *Br. melitensis* infections) agglutinins persisted for four years after recovery, *in 60 per cent. for four to five years, and in 50 per cent.* for six to seven years. On the other hand Carpenter and Boak [49], Huddleson and Johnson [178], Parsons and Poston [284], and Robinson and Evans [309] have testified to the complete absence of agglutinins in some definite cases of undulant fever (6 per cent. of Carpenter and Boak's cases), and, as I have remarked, there were two such cases in my series Birt and Lamb [24] had a fatal case with fever up to 104°F., in which the titre never rose above 1 in 100.

It is important to note that specific agglutinins take at least five days to develop and usually a week, that they may take as much as a year to appear, as in one of my cases, that a high titre at the beginning of a long illness may completely disappear and then reappear [223], and that the titre may rise after the apparent complete recovery of the patient (in my CASE 157 *the titre had risen to 1 in 1,250, three months after recovery, from an initial 1 in 250).*

With regard to the true significance of this evidence as to the persistence of agglutinins in patients who have apparently recovered from the disease, *our conclusions will be influenced by our views* as to the frequency with which *Brucella* infection persists in the body, giving rise to no subjective symptoms or objective signs, with the exception of a positive agglutination test, *but liable at any* interval to cause a true relapse with bacteraemia [pp. 136, 138] Personally I believe that such cryptic infection is far commoner than is usually supposed *The value of positive agglutination is much* increased if repeated tests show a rising titre.

It will be seen from all this that a *single negative agglutination test should never be taken as evidence of the absence of Brucella infection,* but that in suspected cases repeated tests should be made. It is also most important that the test should be carried out over a wide range of dilutions (up to 1 in 1,280), because of the *very common prozone*

ıenomenon [77, 147, 154, 319], in which, owing to the presence of complete or blocking antibodies, agglutination is prevented, sually in the lower dilutions. The Expert Committee in its third port [197] has recommended the use of 5 per cent saline as a luent in the test, to reduce the number of possible false negative eactions

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everal times, and then reincubating after the addition of antiuman globulin made in the rabbit This test is sometimes useful nd various modifications of it are also employed [345, 374].

An important point, raised many years ago in connection with nfection from milk, is the possibility of the presence of agglutinins n the blood being due to their absorption or that of dead *Brucellae* n the food An elaborate investigation to test this possibility was arried out by McCullough *et al* [232] on volunteer convicts The olunteers were all carefully selected to exclude previous *Brucella* nfection or exposure to *Brucella* antigens and were given for prolonged periods heat killed *Brucella* vaccine by the mouth All results were completely negative and the authors concluded that the prolonged feeding of heat killed *Brucella* to healthy individuals does not produce significant quantities of agglutinins or dermal sensitivity

Finally there is the question of non-specific agglutination of a *Brucella* antigen Improvement of the quality of *Brucella* antigens has eliminated many causes of false positive reactions, but crossagglutination in cholera and tularaemia still remain As regards cholera, it is now known that *Vibrio cholerae* and *Brucella* share their H antigen, so that, as McCullough says [229], 'the majority of individuals receiving the standard immunisation against cholera [illegible]

showing no disease diagnosable as undulant fever and with titres of 1 in 10 to 1 in 40, the onset of such diseases as pertussis, varicella, '*β-haemolytic streptococcal tonsillitis*', etc, sent the titre to *Brucella* right up, in one instance from 1 in 80 to 1 in 640 in one week. Jordan [198] recorded falls in titre in four patients who were apparently well, in one case an initial titre of 1 in 160 was unchanged after eight months, whilst in another an initial titre of 1 in 320 had completely disappeared in the same period. Molinelli [258] found that in 80 per cent. of brucellosis cases in Argentina (mostly *Br melitensis* infections) agglutinins persisted for four years after recovery, in 60 per cent. for four to five years, and in 50 per cent for six to seven years On the other hand Carpenter and Boak [49], Huddleson and Johnson [178], Parsons and Poston [284], and Robinson and Evans [309] have testified to the complete absence of agglutinins in some definite cases of undulant fever (6 per cent. of Carpenter and Boak's cases), and, as I have remarked, there were two such cases in my series. Birt and Lamb [24] had a fatal case with fever up to 104°F., in which the titre never rose above 1 in 100.

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[illegible]

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It is very important to note that the intradermal injection of a *Brucella* antigen for the skin test will often provoke the formation of agglutinins [52], thus obscuring the diagnosis.

A test was introduced by Coombs [75] in 1945 for the detection of weak and incomplete Rh agglutinins This test was later modified for the detection of similar *Brucella* agglutinins, the sensitivity of the agglutination reaction being increased by removing the supernatant fluid after the usual incubation, washing the deposit with saline several times, and then reincubating after the addition of anti-human globulin made in the rabbit. This test is sometimes useful and various modifications of it are also employed [345, 374]

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cent. to 1 in 40 or higher; and 20 per cent. to 1 in 80 or 1 in 160. In the group tested, eighteen to twenty-eight months after vaccination, 27 per cent. still had titres of 1 in 40 or higher.

Cross-agglutination of *Brucella* and *Pasteurella tularensis* was demonstrated by Francis and Evans [129] (the resemblance of the two organisms has been referred to on p. 13), who concluded that cross-agglutination between these organisms was so frequent that sera from cases suspected of either infection should be tested for both, unless the clinical history pointed definitely to a recognised source of infection for tularaemia or undulant fever; secondly that a serum showing a marked difference in titre for *P. tularensis* on the one hand, or *Brucella* on the other, could usually be classed by the higher titre as due to the organism giving this; and thirdly that where the titre was the same, or nearly the same, agglutinin absorption tests should be done. Beatty [17] reported that 102 out of 130 of his undulant fever patients had agglutinins for *P. tularensis*, but the diagnostic criteria he used are rather obscure.

Though, as I have indicated, there is no unanimity about the interpretation of the agglutination test, the general consensus of opinion was expressed in the Second Report of the Expert Committee [196] (which was confirmed by the Third Report [197]) as follows: 'the sero-agglutination test, when carried out with a suitable antigen and a satisfactory technique, almost always gives *significantly positive results in the presence of active infection* Repeated tests should be carried out in cases giving low titres or [illegible] brucellosis as unlikely. In cases [illegible] ising agglutination titre [illegible] tion. While high titres indicate a high probability of infection, this does not exclude the possibility of infection in cases with low or no demonstrable titre.'

SURFACE FIXATION

Castañeda [58] has recently introduced a test based on an antigen-antibody reaction, in which a loopful of unknown serum is placed on a strip of absorbent paper with a positive and negative control spot, one on each side, each spot being over a previously dried-on spot of special stained *Brucella* antigen. *One end of the strip is then* immersed in isotonic sodium chloride and the rising liquid carries a negative serum (and control) right up the paper, the spot of positive serum remaining fixed. This test is claimed to have remarkable specificity as tested by blood culture.

COMPLEMENT FIXATION

Many workers have tried to determine the value of the complement fixation reaction in undulant fever and it has been claimed that the test is 'absolutely specific' [258], that complement fixing antibodies appear before agglutinins in the blood [377] (though the reverse is often the case), that the test is more sensitive than the agglutination test [189], and that the end-point is easier to read than in the agglutination test [128] In my series it was too little used to enable any estimate to be formed of its value All are agreed that there is no connection between the two reactions The complement fixation test is certainly the more laborious of the two and Wise and Craig [377] concluded that there was no diagnostic advantage in performing this test instead of or along with the agglutination test, a conclusion for which Spink and Kimball [340] have produced additional evidence On this test the Expert Committee, in its Second Report [196], expresses the opinion that 'the complement-fixation reaction has no practical value at present'

OPSONO-CYTOPHAGIC REACTION

The determination of the opsono-cytophagic index as a means of diagnosing undulant fever in man was introduced by Huddleson and his co-workers [179] and has since been fairly widely used, though little in this country The test is based on the increased phagocytic activity of the polymorphonuclear leucocytes against *Brucella* organisms *in vitro* and this activity was shown to be poor in the early stages of the disease, but to increase as recovery progressed [256] That *Brucella* opsonins are formed during *Brucella* infection is generally accepted and it has been shown that they may persist for many years after clinical recovery [184], though the relation of this phenomenon to latent infection is as obscure as in the case of agglutinins. However, the chief claim made for this test, and the various modifications subsequently introduced [194], either alone or more often in association with the intradermal test, is its supposed value in elucidating obscure cases with negative blood culture and agglutination, chiefly cases of so-called chronic brucellosis (p 109) Harris [161], for instance, claims that 'a low or moderate degree of resistance [as shown by this test] coupled with a positive cutaneous reaction in a patient with symptoms suggesting a brucellosis points to an infection from which the patient has not recovered' Many workers have, however, been highly critical of the

value of this test [65, 115, 127] and the Expert Committee in their Second Report express the opinion that 'the opsono-cytophagic test in all its modifications is not suitable for diagnostic use'. The test has not been used in my series

INTRADERMAL TEST

This test is used to detect specific sensitivity to *Brucella* antigens and was first used by Burnet [42] in 1922 as a field test where no laboratory was available He employed as an antigen a broth filtrate of *Br. melitensis* which he called 'melitin'. Many other *Brucella* antigens have since been used, among them Huddleson's 'Brucellergen', which is said to give many false positive reactions [333] The antigen employed in this country is a preparation named 'brucellin', an extract prepared from organisms of the *Brucella* group according to Olin's technique by the Public Health Laboratory Service. The test is carried out by the injection of 0 1 ml. of brucellin into the skin of the forearm A positive reaction is characterised by the appearance, in four to forty-eight hours, of a slightly raised, sometimes tender, oedematous plaque, 2 to 6 mm. in diameter, distinguished by its redness from the surrounding skin. A simple erythema, unattended by oedema, induration or tenderness, which disappears in twenty-four hours, may be regarded as negative. In my series the test was carried out in fifty-five cases and was positive in fifty-one cases (thirty-two positive, fifteen strongly positive and four very strongly positive). All four cases in which the test was negative had positive agglutination as *follows:*

CASE 1065—1 in 5,000 (negative intradermal test done four days *before* agglutination);

CASE 1198—1 in 250 (intradermal test three days *after* agglutination),

CASE 1218—1 in 2,500 (intradermal test sixteen days *after* agglutination),

CASE 1257—1 in 5,000 (intradermal test three days *after* this agglutination test and seven days *after* first agglutination, positive to 1 in 2,000) This patient eventually died from *Brucella* endocarditis

On the other hand the agglutination titre of the four cases in which the intradermal reaction was very strongly positive varied from 1 in 100 to 1 in 2,560 It will be seen from this that there is no

correlation between the results of the two tests, though Levin [219] has reported an inverse correlation, patients with a low agglutinin titre and a history of chronic infection giving the most severe reactions, whilst those with higher agglutinin titres gave weaker reactions It has been claimed that only in a *Brucella* infected patient will specific agglutinins appear following the intradermal injection of a *Brucella* antigen, but I find the evidence unconvincing The test can be negative not only when specific agglutinins are present, but also when *Brucella* is grown from the blood, as in some of Molinelli's [258] cases and my CASE 1257 referred to above Nevertheless the latter event is so rare that in a doubtful case a negative intradermal test may be regarded as reducing very greatly the probability of *Brucella* infection being present, and retrospectively it reduces the probability of a recent febrile illness having been undulant fever

The tendency of *Brucella* antigen, when injected intradermally, to provoke the formation of agglutinins has already been mentioned [p 103], but Elberg's [19, 111] allergen prepared from *Br suis* seems to be blameless in this respect

A positive intradermal test, then, is definite evidence of sensitisation to *Brucella* antigen (fortunately there is no cross-sensitisation with *P tularensis*), but, like the tuberculin reaction, it does not necessarily indicate the presence of active infection It may be of some use in epidemiological investigations to detect the presence of *Brucella* infection in a group, such as a rural community, a meat-packing plant, etc , but even for this purpose it should be used only by experts, and its value for detecting sporadic cases of *Brucella* infection is very slight The Expert Committee in their Second Report [196] say 'a positive intradermal test denotes a specific allergic condition of the individual and should be regarded as free from other diagnostic significance, regardless of the antigen or technique employed, it certainly does not prove the presence of an active infection The chief value of the test is for epidemiological purposes'

OTHER DIAGNOSTIC AIDS

From a consideration of the blood changes in this disease [pp 76–78] it will be seen that a normal leucocyte count, or a leucopaenia, associated with even a relative lymphocytosis in a febrile patient should suggest the possibility of undulant fever, which can then be further investigated in the ways suggested above There are no constant changes in the erythrocytes to help in diagnosis

As regards the *erythrocyte sedimentation rate* my experience agrees with that of Spink [333] that the determination of this rate is of no help in diagnosis, prognosis or treatment.

Stollerman *et al.* [346] have described a test as a guide to the treatment and management of rheumatic fever, which has been used by Spink and his co-workers in the investigation of undulant fever. This is the so-called *C-reactive protein (CRP) determination*, based on the presence of an abnormal protein in the serum of patients with inflammatory conditions, a precipitate being formed with somatic C-polysaccharide of the pneumococcus. Minute amounts of CRP can be demonstrated in human serum by a specific antiserum obtained from rabbits hyperimmunised by repeated injection of purified CRP. Appearance of CRP in the blood is a non-specific but extremely sensitive indicator of an inflammatory reaction. Preliminary studies suggest that the test is positive in bacteraemic patients with *Brucella* infection. It may therefore help in the detection of undulant fever.

SUMMARY

For practical purposes I think the following conclusions as to diagnosis are justifiable.

1. The only certain proof of *Brucella* infection is culture of the organism from the body or its secretions [p. 96].
2. Failing this an agglutinating power of 200 units (or, say, with the suspensions of this country's Public Health Laboratory Service a titre of 1 in 80), or in special cases somewhat lower, can be [illegible] acceptable evidence [pp. 98, 104].
3. [illegible] o be regarded [illegible] resent, but a negative intradermal test is a strong indication, though not an infallible one, of the absence of such infection in the near past or the present.
4. The complement-fixation reaction, though specific, has no place in the routine diagnosis of undulant fever [p. 105].
5. Neither the opsono-cytophagic test by itself, or in conjunction with complement fixation or the intradermal test, is of value in the diagnosis of undulant fever [p. 106].
6. Cases in which the circumstantial evidence and/or the clinical picture are suggestive of undulant fever, but in which neither culture of the organism nor the agglutination test is successful,

should be diligently investigated by repeated blood culture, sternal puncture and agglutination tests, in order to prove or disprove the diagnosis.

7 The presence of an obvious neurosis should not blind the physician to the possibility of a co-existent *Brucella* infection, especially when the case has a long history.

CHRONIC BRUCELLOSIS

ong those who have made a special study of *Brucella* infection e is no subject on which opinions are more divided than on that of so-called chronic brucellosis In the first place these differences depend on the definition given to this term, some defining it as a proved state of infection with *Brucella* which has lasted more than a certain time, Spink [333] suggests more than a year; others, however, would confine the term to a special clinical entity, different from the general run of *Brucella* infections, the evidence for this condition being due to *Brucella* infection in any particular case being of a kind which is unacceptable to those in the other camp

All agree that *Brucella* infection can sometimes persist for a very long time and give rise to symptoms which are not encountered, to any extent, in more acute cases [p 92], and that it may give rise to, or at any rate intensify, a neurosis, and, finally, that diagnostic tests, such as blood culture and serum agglutination, may be negative for a long time but finally clinch the diagnosis.

The really important question is what diagnostic criteria should be applied in such cases, so as not, on the one hand, to withhold treatment which might be helpful or to subject the patient to inappropriate treatment or condemnation as a neurotic, and, on the other hand, to avoid the risk, as Spink puts it, of 'substituting an organic disease for a basic emotional disorder', or of applying futile treatment based on a wrong diagnosis, treatment which 'often will plunge him eventually into further despair and frustration' That true cases can go undiagnosed for years and suffer greatly from such diagnostic failure is well illustrated by the case of Dr Alice Evans, who first proved that contagious abortion of cattle and undulant fever in man were caused by almost identical organisms [p 11], and it is worth while to reproduce the account of her experiences in her own words [114]

'In October 1922 the writer became infected while working on cultures of *Brucella melitensis* received from Phoenix, Ariz For the first nine

months the disease was mild. Medical aid was sought and after examina- [illegible]

Then five years of poor health with complete incapacitation much of the time. Again, medical aid was sought in four successive hospitals. The outcome was always the same, the patient was regarded as "neurasthenic". Finally the impasse was broken by the intervention of another disease which necessitated an operation, during which brucellar lesions were found from which B. melitensis was cultivated. Thus accidentally, at last, *came relief from the misunderstandings which must inevitably arise when* a patient is said to be suffering from imaginary ills These misunderstandings are a feature of chronic brucellosis that tries the patient almost beyond endurance'

That a neurosis may develop in long standing cases is hardly surprising, especially when the correct diagnosis is not made until *late in the disease.*

CASE 934. This patient was a schoolgirl of 17 at the time of onset of her illness in March 1945 (though the onset may really have been in January 1944), *when she began to have frequent nausea, sweating and pain in her* left side A provisional diagnosis of tuberculous abdominal glands was made and she was sent to hospital for examination, where tuberculosis of the spine was suspected on X-ray evidence; but on re-examination a month later was excluded (she may well have had a mild *Brucella* spondylitis at that time). Her symptoms on admission were sore throat, backache, lassitude, fever and some looseness of the stools She had had pain in *the left side of the abdomen for the last three months, with sudden* stabbing pains just below the left costal margin at times. *After two* months in bed in hospital Hodgkin's disease was suggested as a diagnosis. She then went home, but in October of the same year she was admitted to another hospital where she was kept in bed until the beginning of November, when she was allowed up for half a day at a time previous to her discharge and during this period her temperature, which had been very slight, began to swing more *During her time in this hospital she* had some mild attacks of abdominal pain and occasional bouts of diar- [illegible] in the minds [illegible]

was sent to Switzerland for a year and allowed to lead a normal life. A year later she returned home feeling fit and so continued, except for [illegible] becoming so severe that [illegible] 1948, she was [illegible] the left side [illegible]

and general malaise. Blood was taken for agglutination and was positive for *Brucella* to a titre of 1 in 12,500 (negative in low dilutions). On 31 July she was admitted to a third hospital suffering from epistaxis, aching in the legs, knees, hips and left wrist, anorexia and irregularity of the bowels. Her fever was of the intermittent type with daily swings, sometimes up to 106°F. and a disproportionately rapid pulse, an unusual feature. Sulphamerazine was given without effect. In the middle of October as she was still ill she was given injections of T.A.B. vaccine (10 million organisms) and the second injection caused severe rigors and spasmodic movements of the head and arms. She was later given sulphadiazine plus penicillin, with no benefit. I saw the patient for the first time on 26 November 1948 and came to the conclusion that she was suffering from undulant fever but that the spasmodic movements were of psychogenic origin. The patient told me that her present illness strongly resembled one she had had in March 1944, including the strange taste in her mouth [p. 82]. She was intelligent, co-operative and uncomplaining, well-nourished but her skin had a blueish tinge and her hands were cold. On my advice she was admitted to a fourth hospital for examination, where her rectal temperature was found not to rise above 100°F. She was considered to have psychological trouble, but her mother refused psychiatric treatment and she was taken home. In January 1949 she was admitted to a hospital for nervous diseases and in March of the same year to a psychiatric hospital where an electroencephalogram, following an attack of unconsciousness, showed marked abnormality. During her time in this hospital she had a daily remittent fever, rising to 99°-100°F. about 6 p.m., but on one occasion to 102°F. When I saw her on 17 June she was greatly improved in every way and free from symptoms.

Her disease had lasted at least four years three months and perhaps five years six months. Though blood culture (October 1948) was unsuccessful in this case the diagnosis seems hardly in doubt but was difficult to make in the earlier part of the illness, though persistent efforts at culturing the organism from the blood or bone marrow, or persistent agglutination tests, might have given the answer if undulant fever had only been suspected. To what extent the patient's psychological disturbances were due to the long continued failure to diagnose her illness is difficult to determine. In 1922 Bassett-Smith [12] remarked that in its early stages nearly every case of undulant fever had been treated for some other disease before the correct diagnosis was made.

But the case I have described is not representative of chronic brucellosis in the sense in which this term is used by some workers. Thus Griggs calls chronic brucellosis 'that form of the disease which

neither at its beginning *nor during* the course of its whole duratio presents the recognisable, acute picture',[1] a definition which woulc I think, exclude Dr. Evans' case and is perhaps altogether to exclusive, because though, as Beatty says, '*in many cases of undulan* [illegible]

may have occurred months or even years before the onset of the vague ill-health with its elusive symptoms which is finally shown to be due to *Brucella* infection

I would agree with Spink [333] that the use of the term chronic in connection with any other illness denotes 'a continuing state of ill-health as measured in a period of time' and he has chosen a period of more than a year to define his cases of chronic brucellosis, which, of course, creates a category which would comfortably include my CASE 934 and many others in my series, but is quite a different *category from that for which the term is more usually employed* As Alice Evans was the person who first drew attention to the chronic forms of the disease, her description of it is important: 'in severity it varies from a very mild form to a prolonged, *progressive* disease which may end fatally . chronic brucellosis may appear as a sequel to an acute attack or the onset may be insidious The patient may be aware of no illness other than mild symptoms of weakness, nervousness, exhaustion on slight effort, suffocating sensation, palpitation, insomnia, depression, irritability or sense of impending disaster. Fever is usually present in low degree; it may be absent for weeks or months, when the patient may suffer from any or *all* the mentioned symptoms A common feature of chronic brucellosis is the lack of abnormalities to be found in physical examination, except *for occasional splenic enlargement and hypotension.' In fact signs* are generally lacking and symptoms are in no way peculiar to this disease, nor are they constant Harris [163] writes 'fatigue of varying degree is practically the only subjective symptom common to all forms of brucellosis'

That many long continued cases of this disease occur in which diagnosis is difficult seems highly probable from the following considerations

1 The known occurrence of many mild cases which for long eluded diagnosis

[1] *Personal communication.*

2. The isolation of *Brucella* from cases with a persistently negative agglutination test [p 97].
3. The persistence of the infection in many cases, as shown by the facts that
   (a) relapses are very frequent, even with antibiotic treatment, often after intervals of a year or more in which no apparent reinfection has taken place (e g my CASE 606 in which six relapses occurred at intervals varying from six weeks to three months).
   (b) The organism has often been isolated from the spleen, gall bladder, lymph glands, bone marrow, etc [p 96]
   (c) The intracellular habitat of *Brucella* [p 48]
4. The occurrence of specific *Brucella* hypersensitivity in some cases, which gives rise to a train of symptoms very different from those of the acute disease and very baffling until the correct diagnosis is made (these are the cases in which a diagnosis of neurosis is particularly liable to be made)

On the other hand chronic ill-health of the kind described, even following a proved attack of undulant fever, is not necessarily due to a *Brucella* infection, so that the establishment of satisfactory diagnostic criteria is of the utmost importance to avoid chaos, though the non-fulfilment of such criteria should not exclude the diagnosis of undulant fever, but, where the indications are incomplete but suggestive, intensive efforts should be made to prove or disprove the provisional diagnosis.

As has been seen, very long cases are not by any means always of the chronic type as described by Griggs, Harris and others The first case of the disease I ever saw was 'acute' throughout and is instructive, for although its probable duration of forty-seven years is, perhaps, unique, yet its main features have recurred at times in my later cases and in the experience of others.

CASE 1. The patient, a woman of about 60 at the time she came to me in 1929, had suffered from an exactly similar illness since 1886, with the exception of a symptom-free interval of three years, when she was about 50, and a few other intervals of a few weeks only In 1886 she was 17 and lived with her parents in a London suburb Every afternoon, from the beginning, her face and eyes would start to 'burn', this being accompanied or closely followed by a feeling of intense cold over the shoulders and upper part of the back Her eyes felt 'as if full of hot sand' After this had lasted for a few hours she would break into a drenching sweat, so heavy

that she often had to change her nightclothes or underclothes two or three times, and she was never able on this account to accept late afternoon or evening engagements She suffered also from headache, lassitude, depression, nasal and bronchial catarrh, severe pain in the back, marked constipation, persistent insomnia at times and disturbances of accommodation, which eventually forced her to abandon the fine needlework of which she was fond. *After severe attacks there was great exhaustion and* some absent-mindedness In spite of the very objective features of the illness her condition was for years attributed to nerves and her temperature was never even taken until, in her late twenties, she went to Ceylon to visit a married sister, when malaria was naturally suspected and her blood found to be free from parasites In spite of her handicaps she married—she struck me as a woman of much quiet charm and great courage—but she was a widow when I saw her. In 1932 her undulant fever at last came to an end—it has been described as a 'self-limiting disease'[1]—but she was fated not to enjoy such peace for long, as in 1933 she developed diabetes [p. 81], fortunately easily controlled, and when I last saw her in 1936 she was not complaining of her lot.

9

DIFFERENTIAL DIAGNOSIS

PERHAPS nothing illustrates better the extraordinary variety of manifestations of this disease and the consequent difficulty of diagnosis than the enumeration of the 148 different provisional diagnoses made in my cases, the most frequent of which are set out in TABLE 10 below.

TABLE 10

PROVISIONAL DIAGNOSES

	NO OF TIMES EMPLOYED
P U O	160
Influenza	159
Enteric Fever or Typhoid	72
Pulmonary Tuberculosis	45
Paratyphoid	43
Glandular Fever	34
Malaria	27
Rheumatic Fever	15
Cold	13
Lobar Pneumonia	13
Pyelitis	13
Sinusitis	13
Appendicitis	12
Subacute Bacterial Endocarditis	12
Tonsilitis	11
Cholecystitis	10
Bronchitis	9
Virus or Atypical Pneumonia	9
Chill	8
Infective Hepatitis	7
Acute Gastritis	6
Dental Caries	6
Infective Mononucleosis	6
Nerves, Neurosis, or Hysteria	6
Bronchopneumonia	5
Meningitis	5
Septicaemia	5

These provisional diagnoses, and the following less frequent ones, include some which are rather symptoms, signs or conditions than actual diseases (and the most fre[illegible] not a diagnosis at all), but the[illegible] true origin was not suspected [illegible] diagnoses, with the frequenc[illegible]

Pneumonitis, rheumatism, rubella, streptococcal infection (4 each); empyema, mesenteric adenitis, otitis media, pharyngitis, pyelonephritis, reticulosis, salmonella infection, subacute rheumatism, tuberculous peritonitis (3 each); abdominal tuberculosis, acute arthritis, Addison's disease, adenitis, *B. coli* infection of urine, Bornholm disease, cerebrospinal meningitis, debility, diverticulitis, dysentery, fibrositis, Hodgkin's disease, meningococcal septicaemia, mumps, nephritis, osteomyelitis, pernicious anaemia, pleuropneumonia, poliomyelitis, radiculitis, splenic anaemia, rheumatoid arthritis, streptococcal pharyngitis, streptococcal tonsilitis, urinary infection (2 each); acidosis, actinomycosis, acute disc lesion, adenoma of the pancreas, adreno-medullary tumour, agranulocytosis, amoebiasis, anaemia, anaphylactic purpura, angina pectoris, anthrax, carbuncle of kidney, carcinoma of the liver, cerebellar tumour, choroiditis, chronic constipation, chronic pneumococcal pulmonary infection, delayed septic condition, disseminated sclerosis, duodenal ulcer, dyspepsia, epidemic vestibulitis, enteritis, epistaxis, erythema nodosum, farmer's lung, febricula, food poisoning, fracture of lumbar vertebra, general ill-health, hepatitis, Hirschsprung's disease, hypotension, increased cerebral pressure, infective endometritis, intestinal infection, intestinal toxaemia, Koch's adenitis, laryngitis, leptospirosis, lupus erythematosus, malignant disease, mastitis, measles, megacolon, migraine, myositis, new growth of bronchus, optic neuritis, oral sepsis, orchitis, peri-arteritis nodosa, perinephric abscess, perinephric inflammation, polyarteritis, pyaemia, pyloric stenosis, relapsing fever, respiratory infection, sacro-iliac strain, sarcoidosis, sciatica, splenomegaly, spontaneous hypoglycaemia, stomatitis, streptococcal fever, streptococcal septicaemia, subarachnoid haemorrhage, subphrenic abscess, sun fever, temporal arteritis, thrombocytopenic purpura, thyrotoxaemia, tracheitis, tuberculous adenitis, tuberculous infection of kidneys, tuberculous meningitis, tuberculous pleurisy, tuberculous spondylitis, tuberculous synovitis, upper respiratory infection, urethritis, and vagotonia (1 each).

Two provisional diagnoses (before that of undulant fever) were made in seventy-eight cases, three in twenty-three cases, and more than three in nine cases (four diagnoses in seven cases; five in one case, and seven in one case)

It is worth noting that appendicitis was diagnosed in ten cases, so that all these patients may be considered to have been in danger of unnecessary operation, as well as a case diagnosed as infective endometritis in which operation was called off at the last moment

A few of the diseases for which undulant fever has most commonly been mistaken in my series, or which have other special claims to notice, will now be considered in detail to see how they may be excluded.

INFLUENZA

Influenza has a more sudden onset than that usually encountered in undulant fever and the generalised pains and postorbital headache are also usually more severe in the former disease. The swinging temperature and heavy sweats occurring at the same time daily should suggest undulant fever, which can usually be confirmed by blood cultures or serum agglutination Perhaps the most striking clinical difference in the two diseases is the severity of symptoms out of proportion to the fever in influenza, and the reverse in undulant fever, in which also disappearance of symptoms is usually rapid when the fever ceases Catarrhal features, which are seen in most cases of influenza at some stage, are uncommon in undulant fever.

TYPHOID FEVER

Typhoid may be suspected in the early stages of undulant fever, especially in countries in which the causative agent is *Br melitensis*, but the undulant fever patient is usually less ill and toxic The chief distinguishing features, however, are the intermittency and irre- [illegible]

obstinate constipation is commoner than diarrhoea, the typical swollen abdomen of typhoid is rare in the other disease, the moist, swollen and furred tongue usually seen in undulant fever is rare in typhoid, as are joint affections, and, finally, enlargement and tenderness of the spleen and liver are far more marked in undulant fever Isolation of the causative organism will clinch the diagnosis and specific agglutinins will usually be present by the end of the first week and, though previous vaccination against the enteric group

(and this is true, of course, of the new antimalarial drugs as well). Also 'in undulant fever of an intermittent type the temperature rises so steadily and slowly that the patient often makes no complaint, or complains of but slight headache and general malaise There is no paroxysm and rarely any attempt at a rigor, though when the temperature falls profuse and continued sweating may take place.' Rigors, however, are, as we have seen, not uncommon in this country (35·4 per cent. of my cases had them) Where malaria and undulant fever co-exist, the malarial parasite will be found in the blood and if, when it is driven thence by appropriate treatment, the fever still persists, undulant fever may reasonably be suspected.

RHEUMATIC FEVER

This resembles undulant fever especially in those cases in which the onset is preceded by irregular pains in the joints, slight malaise and sore throat The ordinary febrile symptoms, such as anorexia, constipation, thirst and chilliness, are common to the onset of both diseases. Moreover, profuse, sour-smelling sweats are also a feature of both and coincide in each case with a remission of the fever In rheumatic fever the anaemia is usually more pronounced and develops more rapidly and the joint affections are generally more definite and painful (though in *Br melitensis* infections this distinction is not always valid) The cardiac involvement, almost universal in acute rheumatism, is unusual in undulant fever

APPENDICITIS AND CHOLECYSTITIS

These are conditions which may both be due to *Brucella* infection, though such infection appears to be usually more transient in appendicitis than cholecystitis, but whether there is actual infection of these organs or not, undulant fever patients with pains in the [illegible]

localising symptoms made a chronic *Brucella* infection of the gall bladder probable

SUBACUTE BACTERIAL ENDOCARDITIS

This is sometimes due to *Brucella* [pp 49, 154] and only culture of the causative organism from the blood will serve to distinguish

Brucella endocarditis from that due to the commoner causative agents, at least in the patient's lifetime.

DISSEMINATED (MULTIPLE) SCLEROSIS

This must be mentioned in passing, as Kyger and Haden [214] suggested that there might be a causal relationship between this disease and undulant fever. This suggestion was based on a review of 560 cases of chronic brucellosis, in whom definite sensory and motor disturbances of the second, sixth or eighth nerves were found, two additional patients having the fully developed picture of disseminated (multiple) sclerosis. The authors then carried out intradermal tests with Brucellergen, confirmed in about half the cases by Foshay's antiserum reaction, on 118 consecutive cases of disseminated sclerosis at the Cleveland Clinic and found 96 per cent. of the patients positive for *Brucella* infection by the Brucellergen test, and an even higher percentage when the antiserum reaction was used. However, as Spicknall *et al* [329] pointed out, though two out of 560 cases diagnosed as chronic brucellosis are said to have had disseminated sclerosis, and this is more than would be expected, yet the numbers are too small to carry conviction Moreover, *Brucella* infection might well produce symptoms *resembling* disseminated sclerosis, and in any case the diagnosis of *Brucella* infection was based on Harris' criteria [163], which are not generally accepted Eisele and McCullough [109] investigated the question directly by examining fifty-two patients, diagnosed as suffering from disseminated sclerosis by the neurologists of the University of Chicago Clinics, by means of the agglutination, opsono-cytophagic and intradermal tests (Brucellergen) and found no evidence of immunologic or allergic response to *Brucella* antigens

HODGKIN'S DISEASE

Though Hodgkin's disease was the provisional diagnosis in only two of my cases [p 110], it calls for mention because fever, adenitis and splenomegaly occur in both diseases, and granulomata are found in the diseased tissues in both conditions In Hodgkin's disease, however, the adenitis is more marked, and progressive enlargement of the mediastinal glands, with consequent cough, dyspnoea and cyanosis, is very rare in undulant fever. But quite apart from possible mistakes in diagnosis the two diseases may co-exist [125, 284, 333, 378], and this has given rise to the suggestion that *Brucella* may be

the causative agent in the other disease. Investigation of this hypothesis by Spink's team [333] failed, however, to establish any aetiological relationship

NEUROSIS

Finally, the relationship of *Brucella* infection to neurosis is very important to remember when considering the differential diagnosis This question has been treated at some length under the heading of chronic brucellosis [p 109]

PREVENTION

ERADICATION OF ANIMAL RESERVOIRS OF INFECTION

THE most important preventive measure is, of course, the elimination of the animal reservoirs of infection In Great Britain this means the eradication of contagious abortion of cattle and the declared policy of the Government has been the reduction of infection by calfhood vaccination with S 19 vaccine, and although there has never been any official plan for eradication on the basis of blood tests, it is widely believed that vaccination will eventually be followed, when the incidence of abortions has been sufficiently reduced, by slaughter and compensation.

Various investigations suggest that the percentage of pregnancies ending in abortion has been reduced from about six in 1946 to about two in 1950. The proportion of milk samples containing *Brucella* has not decreased to the same extent and the Central Veterinary Laboratory of the Ministry of Agriculture, Fisheries and Food found *Brucella* in 7·5 per cent. of 665 samples from individual cows and 18 5 per cent of 3,108 bulk samples, for the year 1951–2

The number of cases of undulant fever reported to me, from roughly the same sources as before (Public Health Laboratory Service, Medical Officers of Health, private practitioners, hospital doctors, etc), has remained pretty steady This might be due to chance, as there is no compulsory notification of undulant fever, or [illegible]

improved diagnostic methods I have no doubt that there has been some increased awareness of the disease, though I have at times been disappointed at the limited success of my efforts in this direction, just as I have at the readiness with which the possibility of *Brucella* infection is often rejected

As regards *Brucella* infection in other animals, the problems presented by such infection in sheep, and even more so in goats, in many backward countries, are formidable owing to the unhygienic mode of life of the peasants [p 44], the obstacle to effective

eradication presented by poverty, the difficulties of diagnosis and the lack, hitherto, of vaccines effective for these animals. There seems now to be a good prospect of closing the last gap, as several preventive vaccines have been devised for goats which show great promise [197]

Whilst waiting for the elimination of these animal reservoirs much can be done to prevent the conveyance of infection from animals to man

AVOIDANCE OF INFECTED FOODS

In Great Britain the most important food to avoid is milk which has not been effectively heat treated, a counsel of perfection which will never be completely obeyed until *all* milk in this country is pasteurised. Though pasteurisation has been gradually and considerably extended during the last thirty years, shortage and expense of apparatus, but above all ignorance, prejudice and the obstruction by vested interests, have effectively held off universal compulsory pasteurisation.

A common misunderstanding which has, I believe, played an important part in the infection of individuals and obstruction to the policy of universal pasteurisation, has been the conception of *safe* milk. Thus it is generally believed that tuberculin tested milk is synonymous with safe milk, and this illusion has been fostered by the Government drive, admirable in many ways, for the attesting of herds Though the establishment of such herds, virtually free from tuberculous infection, is in every way laudable, and though the owners of such herds may be expected in their own interests to take special trouble to avoid *Brucella* infection as well, yet the consumer of milk from such herds has no guarantee that it is free from *Brucella* and, as I have shown [p 36] many persons have been infected by milk from tuberculin tested herds and still are. It should not be, but unfortunately still is, necessary to insist that efficient heat treatment (and of course subsequent clean handling) of milk is the *only* guarantee of its freedom from *Brucella* and many other pathogenic micro-organisms

Cream is often overlooked as a source of infection [p 39] but is liable to contain a greater concentration of *Brucella* than the underlying milk. It cannot be too often reiterated that any person consuming raw milk or cream, even a small quantity and on a single occasion, is liable to contract undulant fever, which, though unlikely to kill him, may give him months or years of ill-health

Fortunately *Brucella* is killed by a lower time-temperature combination than the tubercle bacillus, the killing of which has always set the standard for pasteurisation, so that milk pasteurised in accordance with the official standards in this and many other countries will not contain living *Brucella*. It is, in fact, sufficient for this purpose merely to raise the milk to the boiling point and then cool it immediately.

Cheese has not been shown to be a source of infection in Great Britain, but in many countries fresh goat's milk cheese is a very important source [p 39]. In such countries the elimination of this danger presents a very difficult problem, as universal pasteurisation is impracticable and heat-treatment of the cheese has so far been shown to change its character so greatly as to render it unacceptable to the consumer. Therefore pending the elimination of infection from the animals supplying the milk from which such cheeses are made, the only useful measure seems to be propaganda to warn people of the danger inherent in the consumption of these cheeses.

Workers in meat processing plants, especially in districts where *Br. suis* infected animals, or their meat, are handled, should be warned of the danger of consuming the uncooked sausage meat, etc., whilst thorough cleansing of the hands before taking food should be advocated for all persons handling infected animals or their products

OCCUPATIONAL PRECAUTIONS

As has been shown [pp. 42–44] veterinary surgeons, farmers and farm workers, slaughter men, etc, are exposed to special risks of *Brucella* infection, risks which can be reduced, though seldom abolished, by certain simple precautions. Thus the increasingly common wearing of long rubber gloves by veterinarians when delivering the foetus or after-birth of infected cows appears to be effective in reducing infection, or at any rate arm rashes. For laboratory workers great care in handling cultures of *Brucella* is obviously important

PREVENTIVE VACCINES

Whilst S 19 vaccine has proved helpful for cattle and the prospects of developing preventive vaccines for sheep and goats look more promising than ever before, a satisfactory corresponding vaccine for man has not yet been developed For countries where the chief source of infection is milk, or where contagious abortion, and with

readily available at small cost to the farmer, the responsibility should be placed fairly and squarely on his shoulders and the public thus protected from undulant fever and other milk-borne infections. It is argued that the cow excreting *Br. abortus* in her milk cannot be detected by clinical examination, but so long as pasteurisation is not universally compulsory the dairy farmer might reasonably be expected to protect the consumers of his milk, either by keeping his herd free from *Brucella* or by voluntarily pasteurising his milk. The fact that it is being found increasingly difficult to secure supplies of fresh milk in many rural areas is an argument rather for a survey of the whole milk problem, of which freedom of the milk from pathogenic organisms is an important part, than for allowing this source of infection with *Brucella* (and other pathogens) to continue.

Firstly, as regards the psychological aspect, it is of great importance to the patient's morale to establish a definite diagnosis as soon as possible and then to assure him that this is a self-limiting disease, which, even without the help of drugs, often comes to a sudden end when such a result is least expected, whilst the remedies now available have in most cases *greatly reduced the duration of the illness*. At the same time it is unwise for the physician to give any exact estimate of the duration of the illness for the reasons given later in Chapter 12

Rest in bed is indicated in all but the mildest cases as this will reduce the feeling of exhaustion which is so common, limit the fever and sweats, and lessen anorexia and pains and aches.

In a disease such as this which, on account of its long duration, *frequency of relapses* and *usually attendant anorexia and feeling of weakness*, has a most depressing effect on the patient—though curiously enough once the host-parasite balance has been restored recovery is usually surprisingly rapid—supportive treatment is of great importance Thus the patient should be encouraged to eat as sustaining food as his digestion will allow and not be confined to slops; his nightwear and bedding should be changed whenever heavy sweats occur, as they so frequently do, and symptomatic treatment for *headache, muscle ache, constipation, cough, sore throat*, etc., should not be neglected. Antipyretics should be avoided owing to their depressing effect and encouragement of sweating; headache, etc , being treated with codeine or other suitable drugs. In long continued cases and in convalescence, especially from *Br. melitensis* infection, massage is useful for restoring the circulation and the tone of the muscles Anaemia should be treated along the usual lines

When the fever has subsided the patient should be encouraged to get up, and in fact in many of my cases in which the patient has had a persistent temperature of about 99°F. the remaining fever has been banished as the result of increased activity. At the same time he should be warned of possible relapses, for which he should seek treatment immediately Though, as I have remarked above, symptoms often come to a sudden end quite apart from treatment, yet in many cases some persist for a while after the disappearance of pyrexia

SPECIFIC TREATMENT

Though antibiotics, with or without sulphonamides, now constitute the standard treatment for most cases of this disease, it will be well first to consider for a moment other treatments employed before the introduction of antibiotics.

Almost every known drug believed to have a bacteriostatic or bactericidal effect has been tried at some time in this disease and when I gave my Milroy Lectures in 1950 [84] I found I had records of seventy-nine such remedies Of these the only one which had proved at all effective was protein shock

PROTEIN SHOCK

This treatment was usually given by the injection of T.A B vaccine (prepared from organisms of the enteric group), used not as a specific but merely as a convenient means for producing pyrexia. It led to apparent recovery in twenty-two out of forty-two cases in which it was tried, but only when a marked general reaction, with a temperature of 102° to 104°F (38 9° to 40°C) had been produced by its injection. The dose usually employed was 25 to 75 million organisms at intervals of three to six days or more, injected intramuscularly (intravenous injection is even more effective, but the extra risk does not seem to me to be justified) Though the effectiveness of this treatment was presumably mainly due to the pyrexia produced, it may also have been connected with an expulsion of *Brucella* into the blood stream from their lairs in the reticulo-endothelial system, as I have found this method useful in securing a positive blood culture after previous negative attempts Basso, Miyara and Molinelli [13] found protein shock given with a *Brucella* vaccine far more effective than with non-specific vaccines

Owing to the necessity of producing a marked general reaction, if this treatment is to be effective, it is contraindicated in infants or very old people and in those with cardiac or renal insufficiency

Protein shock might, I think, be considered in those cases in which antibiotics have given only temporary relief or the patient is intolerant of them, but if the symptoms suggest *Brucella* allergy, desensitisation [p 148] would be more appropriate

SULPHONAMIDES

From the days of Prontosil every new sulphonamide has been tried in turn and all degrees of success and failure recorded The general

opinion at the present time, with which I concur, is that no sulphonamide by itself is sufficiently effective to be worth while. On the other hand various combinations of sulphonamides with antibiotics have been employed with success, though the part played by the sulphonamide partner seems to me obscure.

It will be most convenient to consider such combinations after dealing with the antibiotics.

ANTIBIOTICS

That the introduction of the antibiotics revolutionised the treatment of undulant fever, by shortening the course of the disease and reducing complications and deaths, no one with experience of undulant fever before their advent would deny [p. 94], and the reduction in the duration of fever which was achieved in my series is shown in TABLE 11.

TABLE 11

DURATION OF FEVER IN 341 CASES TREATED WITH ANTIBIOTICS AND 874 CASES NOT SO TREATED, EXPRESSED AS A PERCENTAGE OF THE TOTAL CASES IN EACH GROUP

	WEEKS										YEARS		
DURATION OF FEVER	LESS THAN 1	1	2	3	4	8	12	16	20	24	1	2-3	MORE THAN 3
Treated with antibiotics	5.3	11.1	15.0	12.6	25.5	9.7	4.4	2.9	1.2	6.2	2.9	0.6	2.6[1]
Not treated with antibiotics	2.1	7.7	8.8	10.1	25.9	17.9	9.8	5.1	2.9	5.7	2.2	0.8	1.0

[1] The duration of fever in this group has been taken at its face value, but the duration from commencement of antibiotic treatment gives a more correct idea. The *total duration of fever* in the 9 cases involved and the *duration after the commencement of antibiotic treatment* (in brackets) were as follows 35 years (36 hours), 14 years (2 weeks), 10 years (6 weeks), 7 years 9 months (2 years), 6 years (2 weeks), 5 years (2 years), 4 years (5 months), 3 years 6 months (4 weeks), and 3 years 4 months (12 months)

At the same time it is of the utmost importance for efficient treatment, and the avoidance of unnecessary suffering and disappointment for the patient, to realise that we still know very little

about the best way of using these powerful remedies, and that there is a considerable, and perhaps growing, number of patients who cannot tolerate certain antibiotics, or, not infrequently, all of them. It is often forgotten, moreover, that the patient's ultimate recovery depends largely on the effective action of his *non-specific defensive mechanisms*, the importance of which is at last beginning to be recognised For these to be given a chance the *minimum effective dose* of antibiotic should be employed and there is some evidence (though not yet sufficient for proof) that in cases which do not respond to treatment within, say, five days, an interval of freedom from treatment of the same length, followed if necessary by a further short course of therapy, has its advantages.

Antibiotic treatment should not be employed automatically in every case. The chief indications for its employment are the severity of the illness, the continuance of fever and other symptoms for more than two weeks with no signs of abating, the presence of complications, and proof that *Br suis* is the infecting species, as this organism is very apt to cause suppuration With children, in whom the disease is usually mild [p 93], the physician should think twice before instituting such treatment, unless there are special indications

Many different individual antibiotics, and combinations of them with other antibiotics or with sulphonamides, and many dosage and time schedules have been recommended by different workers Whilst, therefore, I will give my own experience of those I have employed, I shall try to give, in addition, the main variants which appear to have been successful In assessing the results one should bear in mind the differences due to special selection of cases and special care, the effects of race and environment and the thoroughness of follow-up

CRITERIA OF SUCCESS Before proceeding to consider antibiotic treatment in detail, it is, I think, worth while to examine the criteria of success employed in this connection and to ask the following questions

1 In view of the frequency with which *untreated* cases make a spontaneous and often sudden recovery, at what maximum interval after beginning antibiotic treatment can improvement or disappearance of symptoms be attributed to the antibiotics given? Both long intervals and also recovery (patient afebrile) the day after starting treatment require consideration

eleven days There was prompt clinical improvement in all cases, but in three cases the organism was grown from the blood one to three months after completion of treatment. In consequence the authors recommended a dosage of 4 to 6 G. daily. Spink [333] has, however, subsequently reported a series of sixty-seven cases treated in the University of Minnesota Clinics, thirty-five of them with bacteriological infection and all but two of them infected with *Br. abortus* These patients were given 0 5 G. chlortetracycline four times a day for ten to twenty-one days and of the thirty-five patients with culturally proved infection twenty-three (66 per cent.) recovered and remained well after one course of therapy. With additional therapy following relapse a further nine recovered (total recovery rate 90 per cent.) and only three patients were known to have continued undulant fever.

Debono [94] obtained striking success in twenty-four cases of *Br. melitensis* infection in Malta, giving 0·25 G. every three hours, the first two patients being worked up gradually to this dosage. All except one patient becameafebrile within four days of the full dosage being attained. He had no relapses during observation periods of eight weeks and upwards in ten cases given full treatment for twelve to fourteen days. Similar results were obtained by Molinelli *et al* [265] in forty-six cases in Argentina, the organism being grown from the blood in all cases but one (*Br. suis* in twenty-four cases; *Br. abortus* in twelve and *Br. melitensis* in nine) Aureomycin was given by mouth in seven cases (22 G. in ten days—92 G. in forty days); per rectum in one case (aqueous solution at pH 4·5 containing 7·14 mg. aureomycin hydrochloride per ml diluted with an equal part of physiological saline plus 30 min tincture of opium); intramuscularly in three cases (the same solution but undiluted), and intravenously in thirty-five cases (the same solution but with a pH of 2 8 and content of aureomycin reduced to 5 mg. per ml., the acidity being neutralised with buffer solution before injection). The immediate results were dramatic in all cases but nearly half the patients had relapses, all of which were mild and cleared up with a second course of aureomycin, except for five cases which needed a third course.

On the other hand Killough, Magill and Smith [208] had a relapse rate of 69 per cent in a series of thirty-nine cases treated with aureomycin (11), terramycin (16) and chloramphenicol (12) respectively, in spite of excellent immediate results. In my series [TABLE 12] aureomycin alone was successful in ninety-eight cases

(56 6 per cent.) and combined with streptomycin in fourteen cases (56 per cent)

Aureomycin has also been given by other workers combined with streptomycin or dihydrostreptomycin and Herrell and Barber [168] gave the latter combination to twenty-five patients with culturally proved infection and ten who were clinically typical and had agglutination titres of 1 in 600 or more The dosage was 3 G. aureomycin per diem in doses of 0 75 G every six hours, plus 1 G. dihydrostreptomycin morning and evening, for twelve to fourteen days Of the nine cases with *Br. abortus* infection all were afebrile in forty-eight to seventy-two hours and on follow-up eight to nineteen months later none had relapsed symptomatically or bacteriologically Of the seven cases with *Br. melitensis* infection all but one became afebrile in a few days, the remaining case relapsing six weeks after becoming afebrile The four cases of *Br suis* infection all recovered promptly and were well at follow-up thirteen months later.

Aureomycin has also been given in combination with one of the sulphonamides, but this course does not appear to have any advantage over the administration of the antibiotic by itself Only six of my cases were given aureomycin plus sulphadiazine and of these three were considered successful

OXYTETRACYCLINE (TERRAMYCIN) In the series [208] already quoted [p 134] which were treated with different antibiotics, sixteen received terramycin in a dosage of 75 mg per kg per diem in four-hourly doses with excellent immediate results, though as before stated, the overall relapse rate for the series was 69 per cent Knight *et al* [211] obtained good results in twelve cases with a dosage of more than 5 G per diem, but they think a good deal smaller dose would probably have been effective Relapses occurred in two patients during the three months following treatment and these cases were successfully re-treated with terramycin Knight [210] thinks there is very little difference in the effectiveness of tetracycline and its two derivatives

Of my twenty-four cases treated with terramycin alone, twelve (50 per cent) were considered successful Of another ten cases given terramycin plus streptomycin, only two were successful

Castañeda [60, 62, 64] has introduced a new method of administering terramycin, viz the subcutaneous injection of a preparation of relatively insoluble particles of the antibiotic, which he calls

'amphoteric terramycin'.[1] It was hoped that these particles might come into close contact with the parasite, either by the concentration of the antibiotic, prior to solution, in the lymph glands or spleen, or perhaps by direct or indirect *phagocytosis of the transported* particles by reticulo-endothelial cells. This treatment was given to sixty-eight patients with *Br. melitensis* infection, injections of not more than 160 mg. per week being given. Whereas in the control patients bacteraemia continued uninterruptedly for two to three months, in treated patients there was only 18 per cent. of positive [illegible] after fifteen days and all subsequently became [illegible] treatment with the [illegible] days, 8 mg amphoteric terramycin being given [illegible] three days later, together with dihydrostreptomycin, 0·5 G., intramuscularly twice a day for the first five days, and sulphadiazine, 3 G. per diem, for five days. This course is followed by two days rest, after which the course is repeated omitting tetracycline. Again there is two days rest, after which comes another course and then amphoteric terramycin alone at a dosage of 80 mg. twice a week for three weeks. He recommends that after six months the terramycin should be given alone for six weeks By this method Castañeda claims to have reduced the incidence of relapses to less than 10 per cent. and these relapsing cases are often bacteraemic but asymptomatic

Various other combinations of terramycin with other antibiotics or sulphonamides have been tried, of which the most interesting is [illegible] 500 cases treated by the Health Services in Portugal [illegible] experience the most [illegible] mg. per kg. per diem, for a week or ten days [illegible] per diem on the following days or weeks (two to three weeks for acute cases, or three to four weeks for chronic cases); plus streptomycin, 15 to 30 mg, once or twice a day for the same period (2) In the second method aureomycin was substituted for terramycin. Cayolla da Motta found that the addition of an adequate amount of a sulphonamide to this treatment helped in certain refractory cases but not in

[1] *Method of preparation of amphoteric terramycin* The oral powder is treated with distilled water, centrifuged, filtered through a Seitz disc, the pH adjusted to neutrality by NaOH, the precipitate separated on sterile filter, [illegible] washed with sterile distilled water and dried at 37 C. The powder is then [illegible] of 3-10 microns diameter This preparation, if kept at ordinary [illegible] is fit for use for up to 3 months.

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TETRACYCLINE. This is the most recently introduced antibiotic for the treatment of undulant fever and very few results have been published Spink's [333] preliminary observations suggested that tetracycline was just as effective as its chlor- and oxy- derivatives in the treatment of this disease, and he says that because of its apparent lesser liability to cause side effects it has practically replaced its two derivatives in the clinics of the University of [illegible]

[illegible]

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STREPTOMYCIN AND DIHYDROSTREPTOMYCIN These antibiotics when originally tried singly gave most disappointing results [108, 296, 297] (though Howe and Heyl [175] reported one success), whilst the dosage necessary to produce temporary improvement was usually sufficient to cause serious side effects such as tinnitus, deafness, vertigo, etc It is a curious fact, however, that though sulphonamides by themselves are also singularly ineffective, a combination of a sulphonamide, such as sulphadiazine and

'amphoteric terramycin'.[1] It was hoped that these particles might come into close contact with the parasite, either by the concentration of the antibiotic, prior to solution, in the lymph glands or spleen, or perhaps by direct or indirect phagocytosis of the transported particles by reticulo-endothelial cells. This treatment was given to sixty-eight patients with *Br. melitensis* infection, injections of not more than 160 mg. per week being given. Whereas in the control patients bacteraemia continued uninterruptedly for two to three months, in treated patients there was only 18 per cent. of positive blood cultures after fifteen days and all subsequently became negative. Castañeda [60] has since combined this treatment with the administration of tetracycline at 1·5 G. per diem for five days, 8 mg amphoteric terramycin being given at the beginning and three days later, together with dihydrostreptomycin, 0 5 G., intramuscularly twice a day for the first five days, and sulphadiazine, 3 G. per diem, for five days. This course is followed by two days rest, after which the course is repeated omitting tetracycline. Again there is two days rest, after which comes another course and then amphoteric terramycin alone at a dosage of 80 mg. twice a week for three weeks He recommends that after six months the terramycin should be given alone for six weeks. By this method Castañeda claims to have reduced the incidence of relapses to less than 10 per cent. and these relapsing cases are often bacteraemic but asymptomatic.

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streptomycin (or dihydrostreptomycin), has given good results in the hands of many workers [*108, 260, 320, 337*]. Spink [333] reported a series of thirty-six patients so treated, the dosage eventually being 1–2 G. streptomycin and 6 G. sulphadiazine daily for fourteen days at least. Of the twenty-one patients with bacteriologically proved *Brucella* infection, fourteen made an uninterrupted recovery, but four other patients relapsed after completion of their course of treatment, though they recovered eventually. In three cases though the patients felt better *Br. abortus* could still be grown from their blood on completion of treatment. Of the fifteen patients with negative blood culture before treatment, but every other indication of active disease, only five made a prompt recovery and at least five continued chronically ill

Of my twelve cases treated with streptomycin alone, three made a good recovery [TABLE 12, p. 139], and of six other cases given this antibiotic plus sulphadiazine, three recovered.

The chief drawback of using streptomycin (or dihydrostreptomycin) is its liability to produce side effects, such as dermatitis, purpura, vertigo and deafness (of which the two latter may be permanent), even with a dose of 2 G. per diem It is therefore particularly *important when using this antibiotic to reduce the dose to* the minimum which is effective.

TABLE 12 shows the results obtained in 417 treatments of patients in my series with the principal antibiotics employed. In addition the following other antibiotics were given on less than five occasions each aureomycin plus chloramphenicol plus streptomycin; aureomycin plus chloramphenicol plus sulphamezathine; aureomycin plus dihydrostreptomycin, aureomycin plus sulphamezathine;

phenicol plus sulphathiazole, chloramphenicol plus sulphatriad; erythromycin, streptomycin plus isoniazid; streptomycin plus terramycin plus sulphadimidine, tetracycline plus sulphadiazine, tetracycline plus sulphadimidine, terramycin plus dihydrostreptomycin.

THE RESULTS OF ANTIBIOTIC TREATMENT

The criteria of success I have employed here are as follows: cases in which the temperature was normal before starting treatment, or

12

…ERENT ANTIBIOTICS, ALONE OR COMBINED WITH OTHER ANTIBIOTICS OR OTHER DRUGS, IN THE TREATMENT OF UNDULANT FEVER

ANTIBIOTIC	TOTAL NUMBER AND (PERCENTAGE) RESULT			DOSE IN GRAMMES						NO. OF CASES WITH TOXIC SYMPTOMS AND (PER CENT.)	NO. OF CASES WITH RELAPSES AND (PER CENT.)
				AVERAGE		MAX.		MIN			
	SUCCESS	FAILURE	DOUBTFUL	SUCCESS	FAILURE	SUCCESS	FAILURE	SUCCESS	FAILURE		
Aureomycin	98 (56 6)	28 (16 2)	47 (27 2)	17 0	22 0	80 0	135	1 5	2 0	12 6 9	15 (8 7)
Aureomycin and Streptomycin	14 (56)	6 (24)	5 (20)	29 0 18 5	19 3 12 1	66 0 49 5	39 16	10 0 10 0	5 0 8 0	1	2
Aureomycin and Sulphadiazine	3	2	1	26 7 21 7	27 5 43 5	38 0 32 0	31 56	18 0 8 0	24 0 31 0		1
Chloramphenicol	71 (52 6)	37 (27 4)	27 (20)	25 9	24 1	199 0	120	4 0	1 5	4 (3 0)	16 (11 9)
Streptomycin	3 (25)	9 (75)	0	28 0	8 6	56 0	14	8 0	1 5		
Streptomycin and Sulphadiazine	3	1	2	10 0 27 3	19 5 46 5					1	
Tetracycline	11 (52 4)	8 (38 1)	2 (9 5)	16 1	19 1	49 0	35	3 0	10 0	1	1
Tetracycline and Streptomycin	2	1	2	40 5 18 5	6 0 4 0					1	
Terramycin	12 (50)	6 (25)	6 (25)	16 3	15 9	40 0	31	7 0	3 2		2
Terramycin and Streptomycin	2 (20)	4 (40)	4 (40)	11 5 11 5	18 6 42 0						

in which it became normal on the day of starting, or in which no improvement was noticed until after ten days of treatment had elapsed are recorded as of doubtful significance. Follow-up varied in length from about three weeks to several years. The number of cases with toxic symptoms, presumably due to the antibiotic used, is given but the details are discussed on page 141.

It will be seen from TABLE 12 that, judged by these criteria, the most successful treatment was with aureomycin, or this antibiotic combined with streptomycin, closely followed by chloramphenicol and also by tetracycline and terramycin respectively, but the number of instances in which the latter substances were used is, of course, much smaller. The dosages varied greatly and there can be no doubt that often too much was given. The percentage of relapses recorded was greatest for chloramphenicol (11·9 per cent), but the number depends, of course, on the dosage used, which varied widely, and on the length of the follow-up, among other factors

MINIMUM EFFECTIVE DOSE. I have already [p 131] referred to the desirability of giving the minimum effective dose of any antibiotic and the evidence, at present inadequate, that intermittent treatment may prove at least as effective as continuous bombardment

In TABLE 13 are analysed the data with regard to treatment at limited dosage with a single antibiotic, unassisted by sulphonamides, etc., in my cases.

TABLE 13

THE EFFECTIVENESS OF LIMITED ANTIBIOTIC DOSAGE IN UNDULANT FEVER

CATEGORY		AUREO-MYCIN	CHLORAM-PHENICOL	TERRA-MYCIN	TETRACY-CLINE	STREPTO-MYCIN	ERYTHRO-MYCIN
(1)	Total number of cases given antibiotic	173	135	24	21	32	2
(2)	Number of cases given not more than 10 G	32	9	5	4	1	1
(3)	Total number of cases with temperature normal within a week of starting	77	54	9	10	0	0
(4)	Number of cases in (3) given not more than 10 G	22	9	4	4	0	0

It will be noticed that category 3 includes *all* cases given the antibiotic in question, and not only those in which no more than 10 G. of the drug were given (which cases are shown separately in 4). Thus in thirty-two cases out of 173 (18 5 per cent) given aureomycin, the total dosage was not more than 10 G , and in twenty-two (12·7 per cent.) of these cases the temperature was normal within a week of starting treatment Again in 77 out of 173 cases (44 5 per cent), given very varied dosage, the temperature settled within a week

TOXIC SYMPTOMS FOLLOWING ANTIBIOTIC TREATMENT. The occurrence of untoward effects of antibiotic treatment has been noted by many workers and these effects are of two main kinds

1. direct toxic effects, such as nausea, vomiting, diarrhoea, abdominal pain, etc , and
2. indirect effects due to changes in the nasopharyngeal and intestinal flora.

The effects in the first category usually disappear soon after the antibiotic is discontinued (or even when it is not) Those in the second category include those due to deficiency of the vitamin B series and of vitamin K, stomatitis and pruritus ani, due to the outgrowth of organisms such as *Monilia*, which are disturbing and debilitating for the patient but not otherwise serious, but also long persisting gastro-intestinal disturbances or even, occasionally, severe pseudomembranous enterocolitis due to antibiotic-resistant staphylococci.

The frequency of such effects in my series has already been given in TABLE 12 [p. 139], but they are analysed in more detail in TABLE 14 (excluding stomatitis)

It will be noted that the numbers are small and would no doubt have been even smaller if more moderate doses had always been used (cf Nos 982; 1029, 1367)

As regards the question of sensitivity to antibiotics in general by mouth, it will be noted that though Nos 1315 and 1353 seem to belong to this type, Nos 963, 1238, and 1326 were able to tolerate other antibiotics than the provoking one quite comfortably

Though the evidence given here is too slight for proof, my general impression is that a really large initial dose, at any rate by mouth, is seldom justified

TABLE 14

TOXIC SYMPTOMS FOLLOWING ANTIBIOTIC TREATMENT
(excluding stomatitis)

CASE NUMBER	PROVOKING ANTIBIOTIC (non-provoking antibiotic also used)	DOSAGE	TOXIC SYMPTOMS
963	Aureomycin (Streptomycin)	10 G. in 10 days	Nausea. Indigestion.
975	Chloramphenicol	27 G in 10 days	Urticaria Bad taste in mouth Abdominal pain (splenic area).
982	Aureomycin (Chloramphenicol)	12 5 G. in 9 days (3 G initial dose)	Nausea
1005	Streptomycin	9 G in 9 days	'Great distress.'
1007	Aureomycin	24 G in 14 days (2 G. per diem for last 9 days)	Abdominal discomfort.
1029	Chloramphenicol	18 G. in 8 days (3 G. initial dose)	Nausea Bad taste Diarrhoea Palpitation.
1035	Aureomycin	18 G. in 9 days	Gastro-intestinal disturbances
1238	Aureomycin (Streptomycin Chloramphenicol)	Symptoms after 4 G. in 2 days	Abdominal pain Orchitic pain
1315	Aureomycin	5 G in 5 days	Tremor Abdominal discomfort Dryness of throat
	Tetracycline / Streptomycin	6 G. in 4 days / 4 G in 4 days	Tremor Abdominal discomfort. Dryness of throat
1326	Aureomycin (Terramycin)	2 G in 2 days	Nausea Vomiting
1353	Chloramphenicol / Aureomycin	14 G in 14 days / 42 G in 28 days	Diarrhoea. Malaise. / Nausea. Vomiting
1367	Chloramphenicol	40 G in 14 days	Indigestion. Bad taste Anorexia
	Aureomycin	27 5 G in 11 days	Nausea. Vomiting Dysphagia
1381	Aureomycin	6 8 G in 11 days	Diarrhoea.
1389	Aureomycin / Streptomycin	14 G of each in 14 days	Sore throat Diarrhoea (probably due to aureomycin).

TABLE 14—*continued*

CASE NUMBER	PROVOKING ANTIBIOTIC (non-provoking antibiotic also used)	DOSAGE	TOXIC SYMPTOMS
1478	Tetracycline	49 G in 27 days (symptoms when 3 G given daily)	Diarrhoea
1503	Terramycin Streptomycin	18 G in 14 days 10 G in 10 days	Staph enteritis Intestinal haemorrhage Pyloric stenosis

APPARENT SENSITIVITY OF BRUCELLA TO DIFFERENT ANTIBIOTICS IN INDIVIDUAL CASES Though general statements can be made as to the comparative effectiveness of different antibiotics in *Brucella* infection, yet in individual cases one antibiotic seems to be effective and another (or others) not, and the most effective antibiotic is not always the same Such a proposition is [illegible]

would have shown that the antibiotic given later was not so successful as had been supposed But I have a strong impression that such an explanation is not adequate, though the evidence given in TABLE 15 is not sufficient to prove this and only culture of the organism and testing of its sensitivity could really give the answer

Obviously if one strain of *Brucella* is more sensitive to one antibiotic and another to another (*in vivo*), then if treatment with the first one used is unsuccessful, recourse should be had to another one, but if this is not the case and *all* strains of *Brucella* (or all of any one species) respond uniformly to the different antibiotics, then it is merely a question of choosing the most effective, or least toxic, and pressing it until either it is successful, or failure seems certain, or the patient ceases to tolerate it

There are, of course, cases in which several antibiotics are tried but all fail, such as the following

CASE 1313. A man of 50, whose fever lasted ten months with a greatly enlarged liver and spleen, ascites, severe colicky pains in both loins and tenderness over both renal regions, etc This patient's infection failed to respond to 24 G aureomycin and 31 G sulphadiazine A combination of

TABLE 15

THE RESPONSE OF BRUCELLA INFECTIONS TO ANTIBIOTIC TREATMENT

CASE NUMBER	UNSUCCESSFUL ANTIBIOTIC(S)	TOTAL DOSAGE IN GRAMMES	SUCCESSFUL ANTIBIOTIC	TOTAL DOSAGE IN GRAMMES	LENGTH OF FOLLOW-UP AFTER RECOVERY	NOTES
1003	Chloramphenicol	16 0	Aureomycin	24 0	5 weeks	Severe relapse after 1st treatment.
1044	Streptomycin Sulphadiazine	11 0 50 0	Chloramphenicol	9 0	10 weeks	1st treatment had no effect.
1086	Streptomycin Sulphadiazine	21 0 43 0	Chloramphenicol	33 0	10 days	Immediate and dramatic improvement with 2nd treatment.
1148	Streptomycin	14 0	Chloramphenicol	9 75	3 weeks	
1149	Streptomycin	10 0	Chloramphenicol	15 0	5 weeks	
1165	Chloramphenicol	18 0	Aureomycin	36 0	4 weeks	
1169	Chloramphenicol	35 5	Aureomycin	33 5	8 weeks	Relapsed 9 weeks after becoming afebrile with 1st treatment.
1181	Chloramphenicol	44 0	Aureomycin	42 0	13 weeks	
1193	Chloramphenicol	51·5	Streptomycin Aureomycin Sulphamezathine	17 0 66 0 54 0	12 weeks	Immediate and sustained improvement *from start of* 2nd treatment.
1205	Chloramphenicol	16 0	Aureomycin	45 0	9 months	
1208	Chloramphenicol	28 0	Aureomycin	16 75	7 weeks	
1286	Aureomycin	8 0	Terramycin	12 0	nil	
1363	Chloramphenicol	8 25	Aureomycin	8 25	4 weeks	
1366	Streptomycin	8 0	Aureomycin	15 0	8 weeks	Relapsed 4 weeks *after becoming* afebrile with 1st treatment
1452	Chloramphenicol	4 0	Terramycin	21 0	4 weeks	
1496	Tetracycline	10 0	Streptomycin	20 0	3 weeks	
1498	Terramycin Streptomycin	4 0 2·0	Aureomycin	6 0	4 days	Immediate response to 2nd treatment.
1508	Tetracycline	13 0	Streptomycin	8 0	6 weeks	
1510	(1) Chloramphenicol (2) Streptomycin (3) Tetracycline	4 0 4 0 [illegible]	*Erythromycin*	9 5	4 weeks	Temperature fell to normal within 24 hrs of starting 2nd treatment

streptomycin, 18 G, terramycin, 18 G, and sulphadimidine, 50 G, improved his condition but did not abolish the fever, nor did a further course of streptomycin, 14 G He refused further antibiotic treatment as it made him feel ill and two months after finishing the last course of streptomycin he made a spontaneous recovery

Schmidt [317] found that though chloramphenicol and tetracycline usually made a patient with the acute disease afebrile in a few days, such a result in chronic cases is rare, even when streptomycin is given in addition Moreover, antibiotic treatment does not, in many cases, prevent patients sinking into the chronic phase

CONCLUSIONS The Expert Committee on Brucellosis [197] eached the following conclusions with regard to chemotherapy in his disease:

The tetracyclines alone are more advantageous than the combination of sulphonamides and streptomycin, or dihydrostreptomycin

2 Chloramphenicol is of some value, but caution must be exercised in its use because of the occasional occurrence of aplastic anaemia, for this reason the tetracyclines are to be preferred.

3 If chemotherapy is given it should be for a minimum of twenty-one days, unless the patient cannot tolerate the drugs The use of shorter courses, given intermittently over a period of several weeks, merits further investigation

4. Sulphadiazine, or triple sulphonamides, with streptomycin or dihydrostreptomycin, should be given as follows sulphonamide—daily divided oral dose 4 to 6 G. for twenty-one days, streptomycin or dihydrostreptomycin (or a combination of these two) 1 to 2 G. intramuscularly daily for the same period [1]

5 Tetracycline alone in adults to be given orally in a dosage of 2 G. daily for twenty-one days Children up to 25 kg in weight—50 to 75 mg per kg per diem Children over this weight—adult dosage scaled down on a weight basis

6 For the more severe infections, and for all infections due to *Br suis*, a combination of tetracycline and streptomycin (or dihydrostreptomycin), with or without the addition of sulphonamides, for a minimum of twenty-one days

[1] There seems to be no reason why this treatment should not also be tried in 5 day periods, with the same period of intermission

7. The efficiency of smaller doses of these drugs for the treatment of brucellosis should be further investigated.

CORTICOSTEROIDS

The effect of corticosteroids in lowering host-resistance in the early stages of infection, an effect which is not seen in the later stages of disease, is well known and this encouraged Spink and Hall [336] to try the effect of ACTH in acute toxic human cases. With the intramuscular injection of 25 mg. ACTH every six hours the temperature dropped to normal within twelve to twenty-four hours, toxaemia abated, anorexia disappeared and mental depression gave way to a more pleasant outlook. This improvement occurred even though blood cultures remained positive. Further experience confirmed these findings and the scheme eventually adopted was to inject 25 mg. of ACTH gel intramuscularly every six hours, or to give cortisone by the mouth in a dosage of 50 mg. four times daily. It was found, moreover, that prednisone and 9α-hydrocortisone gave similar results This therapy did not need to be continued beyond seventy-two to ninety-six hours, by which time the patient's condition had [illegible]

[illegible]

[illegible]

streptomycin, of whom forty-five had acute infection and three chronic The organism was grown from the blood of forty-three of the forty-eight patients. The results of treatment were as rapid and dramatic as those described above It is interesting to note that they obtained a higher relapse rate when the cortisone was continued for one to three weeks than when it was given for not more than four days, and that the agglutination titre was apparently depressed by the cortisone, though Spink had found no sign of this Four of their patients had serious side reactions (psychosis, lighting up of tuberculous infection, gynaecomastia, nausea, vomiting, epigastric pain), which emphasises the importance of giving the corticosteroids for a few days only, as recommended by the Expert Committee on Brucellosis [197] who advise ACTH intramuscularly, 40 mg every eight hours, or cortisone orally, 100–300 mg daily (hydrocortisone, 50–100 mg three times a day) If prednisone is used, 20 mg orally three times a day is recommended The Committee warn that *these hormones are potent drugs and should be used only in carefully selected patients, and with extreme caution*

ANTIGENS: IMMUNISATION AND DESENSITISATION

Brucella antigens have been used by many workers for curative purposes (for preventive vaccination see p. 124, and for the use of non-specific vaccines, see p. 129) by two main methods which are often confused owing to our imperfect knowledge of the mechanisms concerned, but which it is important to consider separately. These two methods are immunisation and desensitisation.

The object of immunisation is, of course, to increase the patient's immunity by stimulating the production of antibodies, and consequently it is endeavoured to increase the dose as much as possible, febrile and other reactions being tolerated to a reasonable extent, in order to attain a high degree of immunity. Desensitisation, on the other hand, has as its object the abolition of specific allergy, for which purpose it is important to avoid all general reactions. It is a much longer and more tedious method of treatment, but it is sometimes successful in abolishing symptoms, though not infection, in cases which do not appear to respond to any other form of therapy, and it is a fact well known to the profession that the abolition of symptoms often enables the patient's body to cure itself by natural means. Desensitisation, therefore, is well worth trying both for the comfort it will give the patient if successful and for the assistance it may give to cure.

IMMUNISATION. Many different types of *Brucella* vaccine have been recommended for this purpose, both alone [138, 170, 349] and combined with immune serum [276]. Besides simple vaccines, killed usually with formaldehyde, such variants as detoxified *Alkaligenes abortus* vaccine [276], oxydised vaccine [316], etc., have been devised. Live vaccines have also been used, such as lanolined vaccine [362], and recently large numbers of people in Russia have been treated with live S 19 vaccine, but in view of the known danger to man from this strain [p. 43], and indeed from live *Brucella* vaccine in general [252], and the incompleteness of the information available with regard to this experiment, the Expert Committee did not recommend the routine immunisation of human beings with this vaccine or, indeed, with any living vaccine.

As regards killed vaccines, though success has been claimed for them by some workers [148, 149, 162], others [274] have not been impressed by the results. Much of the evidence for this is founded upon the results of treatment in unsatisfactorily diagnosed cases and some of the results will appear to be more appropriately attributed

to desensitisation than to immunisation. Cayolla da Motta [67] thought the combination of a specific vaccine with antibiotic treatment enhanced the effect of the latter in his cases.

The Expert Committee [197] expressed the opinion that 'there is no proof that such therapy results in bacteriological cure of a patient' and warned 'long continued vaccine therapy is never justified for patients with multiple or vague complaints in which the diagnosis is not proven'.

DESENSITISATION. This treatment has been carried out with many preparations of *Brucella* ranging from crude vaccines to purified antigens. However, the two antigens of which most experience has been gained are Foshay's oxidised vaccine, before mentioned, and Castañeda's *Brucella* allergen MBP.

Scarlett [316] reported on 100 cases of chronic brucellosis, in some of which he claimed to have obtained good results with Foshay's vaccine, but only twenty-five of these patients had positive serum agglutination (only seventeen to a titre of 1 in 80 or over), the diagnosis in the others being based on intradermal tests and opsonocytophagic tests

On the other hand Castañeda's allergen has not only been very carefully controlled as regards strength and purity, but has been tried out on well attested cases. The MBP antigen is prepared from cultures of all three *Brucella* species, washed, ground and killed with 0·2 per cent. formalin in saline. The hypersensitivity of the patient having been tested by intradermal injection of 0·2 ml. of the antigen into the skin of the forearm and, after any reaction has faded, the appropriate initial dose, usually about 0·2 ml, is injected subcutaneously and further injections are given twice a week with gradually increasing dosage but never going above 2 ml, so that by the thirtieth day the patient is generally receiving an average dose. If any injection is followed by a rise of temperature of 1°C. above the maximum temperature of the preceding day, the dosage is not further increased and should, if necessary, be reduced in order to ensure that further injections will not give rise to a significant thermal reaction. It is recommended that this treatment should be continued for one or two months after the temperature has returned to normal Thereafter sensitivity should be tested from time to time, without treatment, the latter being resumed if symptoms reappear

In a series of thirty-five patients so treated [61], of whom

thirty-one were severely ill when first seen, twenty yielded positive blood cultures (*Br. melitensis*) and the remainder had significant agglutination titres All except one had been ill for at least a month and seven for from eleven months to seven years These patients all showed a rapid and sustained improvement following treatment, without any severe reactions, and remained free from symptoms on the average for two months

[illegible]

reactions Such patients cannot justifiably be 'given up as a bad job' until desensitisation has been tried, if the patient is willing, but he should be warned that the process is a long one and liable to occasional setbacks, as is well illustrated by the following case

CASE 1315. The patient was a woman, aged 38 at the time she fell ill For sixteen months her illness was wrongly diagnosed, first as virus pneumonia, and her chief symptoms were sore throat, malaise, fever up to 101°F. (38 4°C), aching all over, constipation, heavy sweating, weakness and an anxiety state She also had sudden 'heat waves' at any time of the day or night, the characteristic bad smell and taste (which was not entirely subjective, as the smell was noticed at times by her son), and occasional rigors and menorrhagia At the end of this time she was found to have an agglutination titre for *Br. abortus* of 1 in 80 and a strongly positive intradermal test Aureomycin not only produced no improvement but caused dryness of the throat, abdominal discomfort, thick coating of the tongue and extreme weakness with shaking of the legs. It was at this point that I saw the patient and advised a combined treatment with tetracycline and streptomycin, but this was equally ineffective and the side effects were more pronounced It was then decided to try desensitisation with *brucellin and she was given a subcutaneous injection of 0 1 ml of a 1 in* 1,000 dilution, which produced a local reaction of 3 cm diameter [p 106] Five days later a second injection of the same size caused a local reaction of 2 25 cm diameter An attempt to increase the dose to 0 75 ml of a 1 in 100 dilution made the patient feel so ill that it was decided to revert to the original dose, which was adhered to for ten further injections, the latter ones causing a rather less marked local reaction In spite of this apparently poor response the patient felt better at the end of this course and was much stronger physically Fourteen months later, as she still had symptoms, she was given a three weeks course of terramycin, without side effects this time, and this produced an improvement, and now six years after the onset of her illness she is pretty well, except for getting tired rather easily and, in her own doctor's words, 'she now really believes

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In a series of thirty-five patients so treated [61], of whom

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Though my own experience of this method has been very slight I believe that it is well worth trying in long standing cases in which antibiotic therapy has proved ineffective or provoked serious side reactions Such patients cannot justifiably be 'given up as a bad job' until desensitisation has been tried, if the patient is willing, but he should be warned that the process is a long one and liable to occasional setbacks, as is well illustrated by the following case

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in her recovery, has lost her neurotic outlook and I think is trying to take her hurdle well'.

[illegible]

was, in the end, the only treatment which could be offered and though its results were slow in appearing and incomplete, in my opinion they contributed materially to the re-establishment of the host-parasite balance.

Pacheco and Pacheco Veiga [279*a*] report great success with desensitisation, for which they claim advantages over antibiotic treatment on the grounds of cheapness, effectiveness in chronic cases, and the absence of any tendency to encourage the growth of more virulent strains of *Brucella*, or of other pathogens.

12

PROGNOSIS

In no disease, perhaps, is prognosis more difficult, owing to the extreme variations in duration, the commonness of a sudden, unexpected disappearance of fever and other symptoms, the frequency of relapses even with antibiotic treatment, and the subsidence sometimes of the acute febrile disease into a condition of vague ill-health

DURATION OF FEVER

Any estimate of the duration of the disease in a particular case must necessarily be provisional owing to the frequently insidious onset, the common history of weeks of ill-health preceding the detection of definite fever or the onset of acute symptoms, and the frequent occurrence of relapses, sometimes at a long interval after apparent recovery It seemed better, therefore, to define *duration* as the total duration of fever so far as can be ascertained, including any afebrile intervals which were not considered to mark recovery followed by reinfection The estimate of duration, as just defined, has been conservative in every case

The duration in the 1215 cases for which it could be ascertained with any certainty is set out in convenient groups in FIG 20

It will be seen that in 400 cases (32 9 per cent) the duration did not exceed four weeks, but that in 503 cases (41 4 per cent) it was between four and twelve weeks, whilst in 127 cases (10 4 per cent) it was over six months and in eighteen cases over three years (viz forty-seven years, thirty-five years, sixteen years, fourteen years, thirteen years, ten years, eight years, seven years nine months in two cases, seven years, six years, five years, four years nine months, four years in three cases, and three years six months in two cases)

The effect of antibiotic treatment in shortening the duration of the fever has been shown in TABLE 11 [p 130]

Quite apart from the duration of fever there is also the length of convalescence, which though usually short, in my experience, can be very prolonged, especially in *Br melitensis* infections Hughes

says that 'while some patients return to duty at the end of a month, many who were invalided to England were away from duty for a

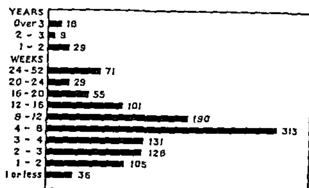


FIG 20. Duration of fever in 1,215 cases of undulant fever

year, others from a year and a half to two years, before final recovery'.

CLINICAL INDICATIONS

In Chapter 7 I have shown how extraordinarily variable is the course of this disease and how deceptive the disappearance of fever and other symptoms may be. Hughes [181], writing of course of *Br. melitensis* infection, remarks that 'intermittent and mild cases vary within very wide limits, while they are unfortunately just the cases which are usually most anxious to know when they may expect to recover', and the majority of cases of *Br. abortus* infection are of this type. Molinelli [258] says that 'there is no symptom by which the physician may recognise the termination of the disease and the beginning of the convalescence', and most workers will agree with Hughes that it is 'never advisable to give an opinion upon the probable duration of any individual case'.

Nevertheless there are certain indications which I have found useful in forming an estimate of the probable duration in individual cases. During a febrile period, the immediate precedence of a stretch of lower fever than has previously been experienced, the return of appetite, the disappearance of headache and sweating, if formerly persistent, and the clearing of the tongue [p 83] are all good signs In an afebrile period the two last signs are also of good prognosis and as the afebrile interval becomes longer than previous

such intervals, the chances of a relapse recede. In cases in which the patient notices a peculiar smell or taste—which is sometimes so characteristic that its reappearance in an apparently healthy patient instantly warns them that their hated enemy is once more upon them—the disappearance of such sensations is of good import

Janbon [188] has found, with *Br. melitensis* infection, that the persistence of adenitis frequently presages an eventual relapse

The persistence of malaise after the disappearance of fever and other symptoms is often a warning that a relapse will occur.

LABORATORY INDICATIONS

The laboratory is not particularly helpful in prognosis, but a rising agglutination titre indicates that the body is building up resistance [illegible]

agglutinins disappear more quickly from the blood than in enteric fever, for instance, and though, as I have indicated [p 127], absence of infection can never really be proved, yet I have noticed that often where a titre of 1 in 200 or more persists for several months a relapse is likely to occur sooner or later In two instances where I warned practitioners of this I received news of the relapse by return of post.

MORTALITY

The case mortality of undulant fever is low in all countries in which [illegible]

and Molinelli [328] 4 per cent for Argentina, Olin [274] 2 2 per cent for Sweden; Zeller [384] 0 6 per cent. for 626 German cases; Beattie, Smith and Tulloch [16] 5 2 per cent for ninety-seven Scottish cases

In my own series there were twenty-four deaths, a fatality rate of 1·6 per cent As will be seen from TABLE 16, three of the patients were over 70 years of age and two more were aged 21 months and 8 years respectively Of the contributing causes of death, one patient

TABLE 16

FATAL CASES OF UNDULANT FEVER

CASE NUMBER	SEX & AGE	DURATION OF FEVER	SPECIAL FEATURES	COMPLICATING FACTORS
52	F 63	17 weeks	Somnolence Intestinal Haemorrhage Jaundice	Nil
78	M 74	5½ months	Rigors Delirium	nil
102	F 32	4 months	Epistaxis Ascites Bronchopneumonia Coma Splenomegaly	? Banti's Disease Splenectomy (end of first month) Cystitis and Pyelitis, following catheterisation
107	M 81	7½ weeks	Occasional Syncope Irritability Depression	nil
182	M 54	6 weeks	Bronchopneumonia	nil
212	F 29	6 weeks	Ascites Uraemia P M Pericarditis, Splenitis, and Splenic Abscess Kidney showed multiple Septic Cysts Heart showed recent Vegetations on Aortic Valves	nil
244	M 67	10 weeks	Mental Confusion Delirium Excitability Dysphasia Jaundice Intestinal Haemorrhage	Dental Sepsis Arterial Degeneration (preceding fever)
292	M 24	8 weeks	Bronchitis Delirium Epileptic Attacks Coma	nil
298	M 67	6 months	Photophobia Sight affected Irritability	Pre-existing Cardiac Incompetence
323	M 47	4 months	Diarrhoea Emaciation Albuminuria, *Haematuria Anaemia Clubbing of* Fingers Presystolic Murmur P M Mitral Endocarditis Embolism of Kidneys and Spleen	nil
366	M 49	11 weeks	Lumbar Pain Rigors Bronchitis Hallucinations Coma	nil
383	M 40	8 weeks	[illegible]	[illegible]
392	F 68	2 years 3 months	[illegible] ptysis	[illegible]
397	M 66	6½ weeks	Visual Disturbances Tenderness over Gall bladder	Long-standing Emphysema and Hyperpiesia
520	M 39	4 weeks	Pleurisy and Bronchopneumonia.	nil
543	M 28	9 months	Eye Ache Rigors	Pulmonary Tuberculosis with Abscesses in Metatarsal and Testis (Probable cause of death—Tuberculosis)
566	M 21 mths	23 weeks	Ls [illegible]	[illegible]
638	F 39	26 weeks	Visual Disturbances Vomiting Tenderness over Gall bladder. Empyema. [illegible]	nil.
806	F 20	[illegible]	[illegible]	[illegible]
920	M 86	[illegible]	[illegible]	[illegible]
1068	M 51	[illegible]	[illegible]	[illegible]

TABLE 16—*continued*

CASE NUMBER	SEX & AGE	DURATION OF FEVER	SPECIAL FEATURES	COMPLICATING FACTORS
1076	M 8	3 weeks	Spleen enlarged Morbilliform Rash Bronchopneumonia. Toxicity Cyanosis. Subcutaneous Emphysema of [illegible]	nil
1238	[illegible]	[illegible]	[illegible]	[illegible]
1257	[illegible]	[illegible]	[illegible]	[illegible]

had pulmonary tuberculosis as well as undulant fever, another had pertussis, a third had *Strep. pyogenes* infection; a fourth had long standing emphysema and hyperpiesia; a fifth and sixth pre-existing cardiac incompetence, a seventh dental sepsis and arterial degeneration, and an eighth a condition which was probably Banti's disease It will be seen, then, that in this series *Brucella* by itself was very rarely the sole cause of death. On the other hand it was and is the cause of much misery and loss of work.

RELAPSES, REINFECTIONS AND IMMUNITY

Relapses, often multiple, are, as we have seen, very common, even with antibiotic treatment [pp 130–141], but in any individual case it may be extremely difficult to say whether one is dealing with a true relapse or a reinfection (see CASE 1, p 113) From the spleen, gall bladder, bone marrow or lymph glands, *Brucella* may make a sortie following a long armistice, which makes the prediction of permanent peace extremely hazardous [172*a*]

[illegible]

at intervals of months or years, and often multiple, with exactly similar symptoms, is very common, attacks which in my cases were sometimes correctly diagnosed at the time, but in ten of them the diagnosis had been missed—over periods sometimes as long as eight years

13

THE FUTURE

MANY years ago Charles Nicolle, the great bacteriologist, and director of the Institut Pasteur in Tunis, used repeatedly to express the opinion that undulant fever was 'a disease of the future', a prophecy which has been amply fulfilled by the discovery in or spread through many countries in every continent of the world. Since his time, however, methods of detecting the infection, understanding of the natural history of *Brucella*, and methods of treatment have all greatly improved. Can we then conclude that undulant fever is on its way out? Personally I believe that any such conclusion would be rash at the present time, though pessimism would also be unjustified.

Thus in Great Britain, as I have pointed out [p 55], though the disease in cattle has been brought under better control, yet the incidence of the human disease does not seem to have been markedly affected.

Even confidence in the absence in this island of all *Brucella* species except *abortus* has been shown since 1940 to be unjustified [p. 19], whilst the known infection of hares and other wild animals, and of birds, on the Continent suggests the possibility of the introduction of new strains from abroad, and the almost unavoidable conclusion that all the three known species and their variants had a common origin suggests that similar mutations may occur at any time, in spite of the apparent stability of the recognised species, with possible consequent increase of virulence or of invasiveness for animal species here that have so far been exempt. This view is, perhaps, strengthened by recent successes in producing variants in the laboratory [p 19].

I have already considered [pp 55–57] the question of the true incidence of undulant fever in this country, but I would repeat here that I am convinced from my personal experience that the diagnosis of this disease is still often missed, sometimes resulting in much

but a confession of past failure. Only when undulant fever

many bewildering guises is made a reality for every medical student will patients be rescued from neglect or the tragedy of being labelled neurotic.

As regards backward countries the difficulties, as we have seen, are so formidable that progress must necessarily be slow. Thus *Brucella* infection is still and will long remain a problem of great importance to most countries of the world, a problem which will tax all the ingenuity, drive and judgement of physicians, epidemiologists, veterinarians and workers in many other disciplines

Great advances have, however, been made in both the animal [illegible]

culture Organization and the World Health Organization, which have set up jointly an Expert Panel on Brucellosis, from which has been drawn an Expert Committee. This Committee met for the first time in 1950 in Washington [195] and they have since met in 1952 in Florence, Italy and in 1957 in Lima, Peru These meetings have been very useful for the exchange of information, the assessment of results, the appraisement of the position, and the issue of recommendations for future research They present a challenge to all interested in the health and prosperity of mankind—to the veterinarian to eliminate the animal reservoirs of infection; to the public health worker to teach people to protect themselves from infection and to explain, with vigour and conviction, to food producers and public authorities the heavy responsibility lying on those who produce, or allow to be sold for consumption, food containing living *Brucella*, to the medical profession to make undulant fever a reality for all medical students, not a curiosity, and to seek out all those who, as undiagnosed cases of undulant fever, are being deprived of effective treatment, mis-treated as cases of other diseases, or ostracised as neurotics, and to give them full and effective treatment, such as the blind administration of a 'wonder drug' can never afford.

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